Advances to improve clinical outcomes and immune function for patients with cancer related fatigue

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積極的緩和醫療能幫助癌症病人活得更好更久

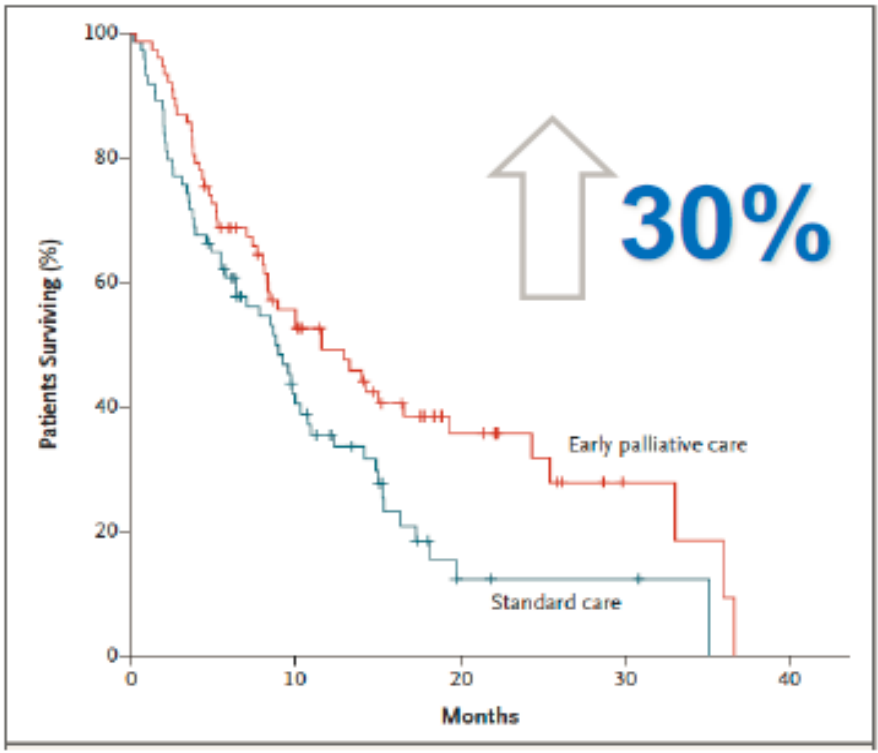
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

	Early Palliative care with Oncologic Care	Oncologic Care	P. value
P't No.	77	74	
Median Survival	11.6 mth	8.9 mth	0.02



N Engl J Med 2010; 363: 733- 42

Symptoms Patterns of Advanced Cancer Patients in NTUH palliative units

Symptoms (range of severity)	On admission			One week after admission		
	n	%[a]	Mean ± SD	*n*	%[a]	Mean ± SD
Fatigue (0–10)	75	97.4	5.8 ± 2.3	68	95.8	5.3 ± 2.6
Weakness (0–10)	76	98.7	5.9 ± 2.3	69	97.2	5.4 ± 2.4
Pain (0–10)	68	88.3	4.6 ± 2.8	60	84.5	2.8 ± 2.0
Anorexia (0–3)	72	96.0	1.7 ± 0.8	59	84.3	1.4 ± 0.9
Nausea/vomiting (0–3)	40	53.3	0.9 ± 1.1	38	53.5	0.8 ± 0.9
Taste alteration (0–3)	27	37.0	0.5 ± 0.7	22	31.4	0.4 ± 0.7
Dysphagia (0–3)	36	47.4	0.7 ± 0.8	30	42.3	0.6 ± 0.9
Restless/heat (0–3)	22	29.0	0.3 ± 0.6	16	22.5	0.3 ± 0.6
Abdominal fullness (0–3)	48	63.2	1.1 ± 1.1	43	60.6	1.0 ± 1.0
Constipation (0–3)	52	69.3	1.2 ± 1.0	54	76.1	1.2 ± 1.0
Diarrhea (0–3)	3	3.9	0.1 ± 0.3	6	8.5	0.1 ± 0.3
Dry mouth (0–3)	41	53.9	0.7 ± 0.8	41	57.7	0.8 ± 0.8
Dizziness (0–3)	38	50.0	0.7 ± 0.7	34	47.9	0.7 ± 0.9
Dyspnea (0–3)	37	48.7	0.8 ± 0.9	30	42.3	0.5 ± 0.7
Insomnia (0–3)	50	65.8	0.9 ± 0.8	39	54.9	0.8 ± 0.8
Night sweats (0–3)	12	15.8	0.2 ± 0.5	10	14.1	0.2 ± 0.4
Anxiety (1–5)	51	72.1	2.2 ± 0.9	50	73.5	2.1 ± 0.8
Depression (1–5)	59	81.9	2.3 ± 0.9	48	69.6	2.0 ± 0.9
Aggression (1–5)	32	45.1	1.7 ± 1.0	25	37.3	1.6 ± 0.9

Tsai SH, et al. Palliative Medicine 2006 : 617-22

不一樣的累……疲憊！

正常人也會累，休息就可改善.....

癌症患者的累，無法藉由休息而改善！

- 累 (Tiredness): 發生在過度活動後，可透過充分休息或睡眠加以改善。
- **疲憊(Fatigue):** 感受異常的累，無法以休息或睡眠緩解，稱為疲憊症。

癌因性疲憊症定義與診斷: NCCN, ICD-10

美國國家綜合癌症網絡[1] (National Comprehensive Cancer Network, NCCN)

與癌症或癌症治療相關而且和近期活動量不成比例的疲累感，具有持續、令人感到不適、而主觀的特性，且足以影響正常生活

國際疾病分類第 10 版 (ICD-10)[2]

符合 A–D 四大要件

A. 症狀	B. 影響生活	C. 引起原因	D. 排除
最近一個月至少有**連續兩週**期間，每天或幾乎每天出現**至少六項 A1–A11 的症狀** (A1 為必需)。	疲累不堪的感覺會**干擾**到職場工作、家務處理、或人際互動。	病歷、身體檢查、或生化檢查有記錄顯示疲憊症狀為**癌症或癌症治療所引起**。	疲憊**不是由精神共病**（如重度憂鬱、身體化疾患、心身症、或譫妄）所引起。

1. NCCN. NCCN Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue, Version 1,.2021.
2. Yeh ET et al. BMC Cancer 2011; 11:387.

癌因性疲憊症的診斷: ICD-10

A

最近**一個月至少有連續兩週**期間，每天或幾乎每天出現**至少六項 A1-A11 的症狀**（A1 為必需）

ICD-10 Code:

R53.0

國際疾病分類第10版 (ICD-10)[1]

A1 **感到明顯的疲累、缺少活力、或需要增加休息，且與近期活動程度不成比例**

A2 感到**全身**虛弱、沉重

A3 感到很**難集中精神**或注意力

A4 感到平常習慣做的事都變得**乏味**而不想去做

A5 感到**難以入睡**、睡得不安穩、早起有困難、或是睡得太多

A6 感到**睡覺起來還是覺得疲累**，精神沒有恢復

A7 感到做什麼事情都必須經過一番掙扎，**勉強**自己去做

A8 因為疲累而感到**悲傷**、失意、或煩躁

A9 因為疲累不堪而事情做一半就**做不下去**了

A10 感到**記性變差**

A11 只要做了**費力的事**就會**持續感到病懨懨、不舒服**

Yeh ET et al. BMC Cancer 2011; 11:387.

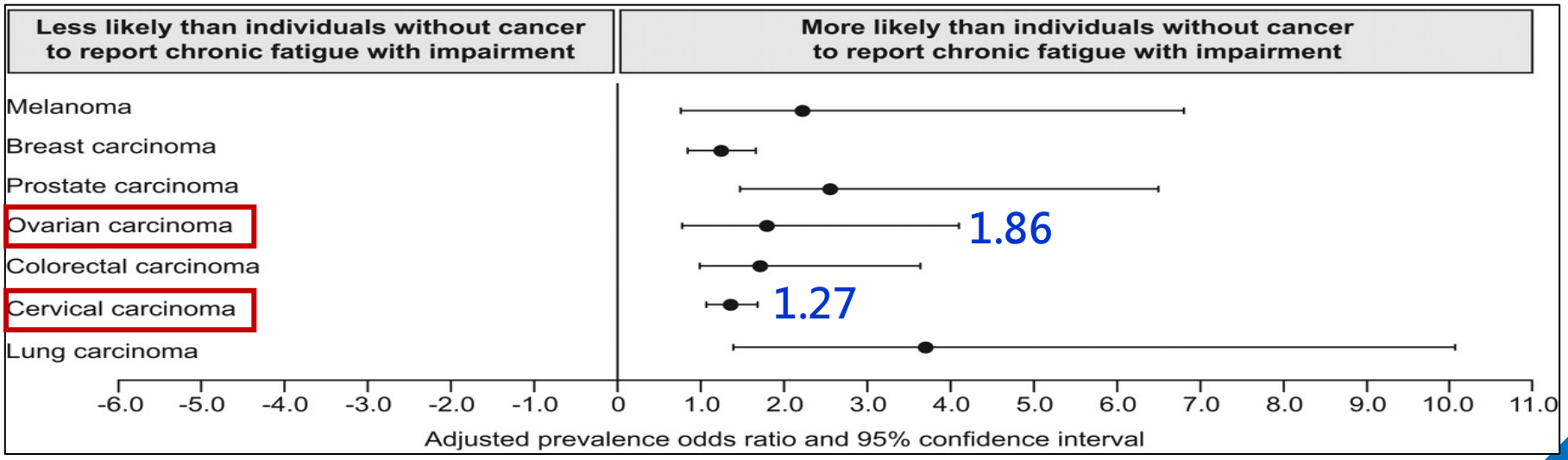
Fatigue疲憊在婦癌盛行率極高，且影響生活功能

- CRF was the **most prevalent symptom** (reported by **93%** of patients) in a qualitative study of **ovarian cancer**, and **severe fatigue** was found in **20%** of patients.

Williams LA et al, J Pain Symptom Manage. 2013; 46:837–45.

Sailors MH et al, Gynecol Oncol. 2013; 130:323–8.

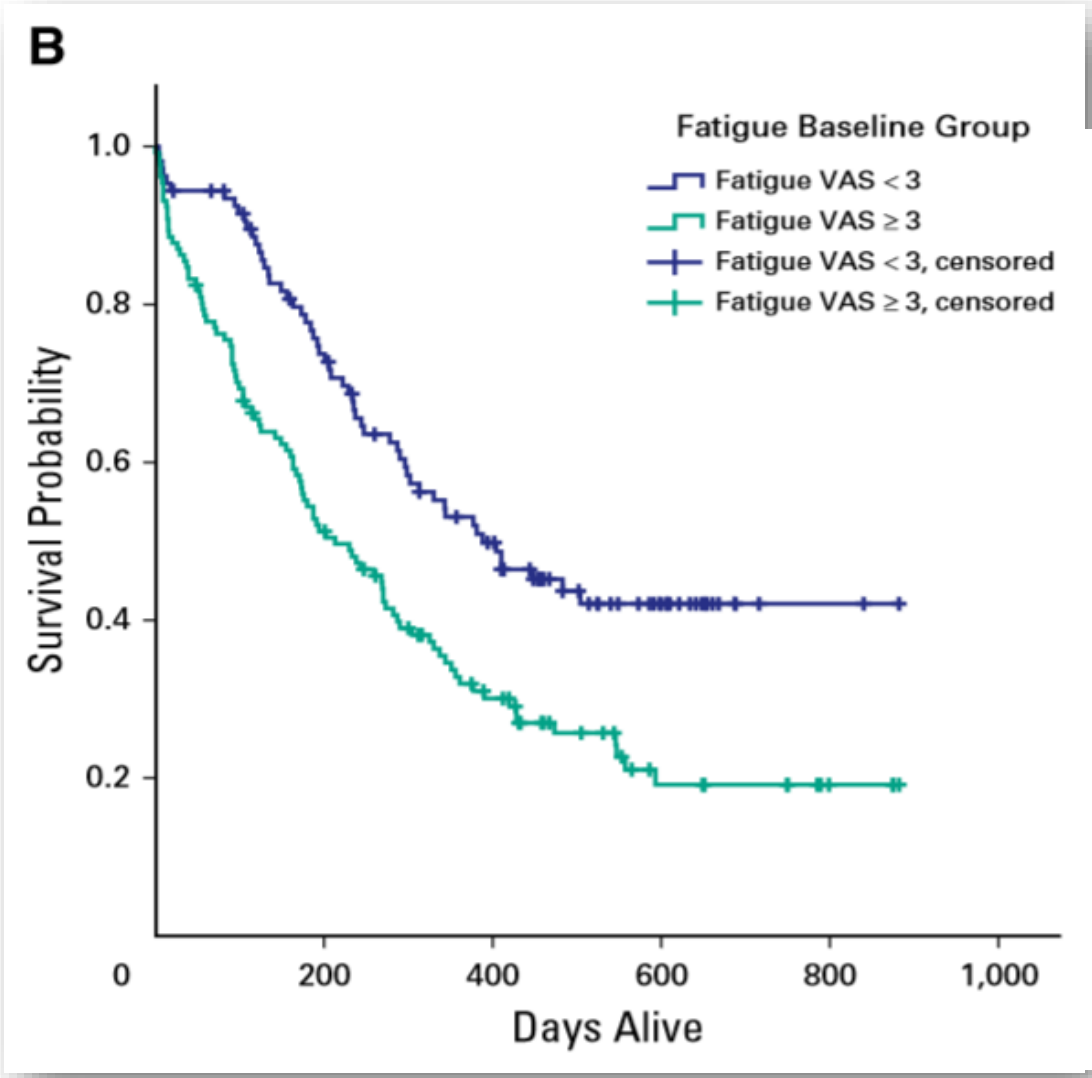
- Patients with **ovarian carcinoma** and **cervical carcinoma** were more likely to report fatigue with some level of **functional impairment**.



Maarten Hofman et al. The Oncologist 2007;12:4-10.

多變數分析顯示在肺癌的病人：

Fatigue與全存活、疾病進展、放射治療反應具相關性

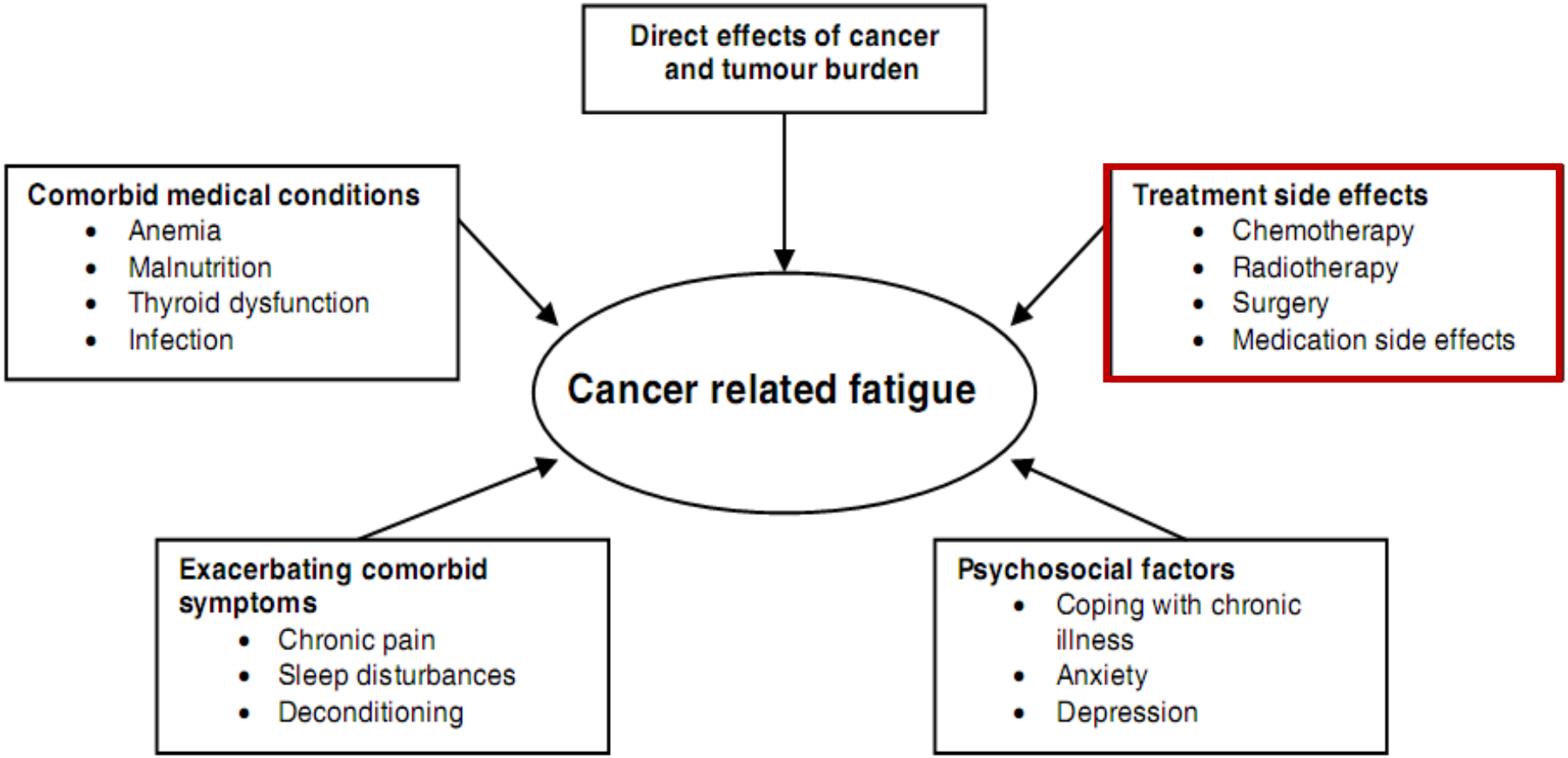


B) fatigue: 388 days (95% CI, 256 to 520 days) for VAS score less than 3 versus 213 days (95% CI, 136 to 290 days) for VAS score > 3 (log-rank P , .001).

* Multivariable analysis for factors affecting **OS, fatigue HR, 1.21** (95% CI: 1.09 – 1.36); Logistic regression analysis for **disease progress, fatigue OR, 1.49** (95% CI, 1.03 - 2.16)

Singh PS et at., Simplified Graded Baseline Symptom Assessment in Patients With Lung Cancer Undergoing First-Line Chemotherapy: Correlations and Prognostic Role in a Resource-Constrained Setting. J Glob Oncol. 2016 May 11;3(1):54-63.

癌因性疲憊症



British Journal of Cancer (2004) 91, 822–828

Fatigue is common at adjuvant chemotherapy for Breast Cancer

	Epirubicin, cyclophosphamide, and paclitaxel plus gemcitabine (n=1565)			Epirubicin, cyclophosphamide, and paclitaxel (n=1567)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	397 (25%)	323 (21%)	204 (13%)	364 (23%)	212 (14%)	200 (13%)
Myalgia and arthralgia	1140 (73%)	200 (13%)	7 (<1%)	1147 (73%)	175 (11%)	11 (1%)
Fatigue	1254 (80%)	198 (13%)	9 (1%)	1287 (82%)	140 (9%)	12 (1%)
Infection	578 (37%)	194 (12%)	8 (1%)	601 (38%)	131 (8%)	10 (1%)
Vomiting	786 (50%)	134 (9%)	9 (1%)	736 (47%)	101 (6%)	7 (1%)
Nausea	1271 (81%)	132 (8%)	0	1255 (80%)	102 (7%)	0

Table 3. Frequency of Patient-Reported Adverse Events During Chemotherapy

	No. of Patients (%)									
	EC-D (n = 994)					DC (n = 1,006)				
Adverse Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	*P*
Nausea	103 (10)	465 (47)	340 (34)	71 (7)	7 (1)	255 (25)	552 (55)	182 (18)	11 (1)	4 (0)	< .001
Fatigue	8 (1)	255 (26)	427 (43)	249 (25)	48 (5)	33 (3)	290 (29)	436 (43)	225 (22)	20 (2)	< .001
Peripheral edema	387 (39)	464 (47)	110 (11)	25 (3)	—	334 (33)	463 (46)	181 (18)	26 (3)	—	< .001

J Clin Oncol. 2017 Aug 10;35(23):2639-2646.

Lancet Oncol. 2017 Jun;18(6):755-769.

大腸直腸癌化療藥物及標靶藥物常見疲憊產生(grade 3/4約10-16%)

Table 2 Examples of Rates of Fatigue With Chemotherapy and Targeted Treatments for Metastatic Colorectal Cancer

Regimen	Line	n	Grade 3/4
Chemotherapy			
FOLFIRI[13]	1	209	10%
FOLFOX-4[14]	1	649	7.9%
XELOX[14]	1	655	5.2%
FOLFOX-4[15]	2	308	8.8%
XELOX[15]	2	311	7.1%
Targeted Therapies			
Aflibercept-FOLFIRI[16]	>1[a]	1226	<5% difference compared to FOLFIRI and <20% in combination arm
Bevacizumab-XELOX/FOLFOX-4[17]	1	1401	Not cited in "adverse events of special interest to bevacizumab"
FLOX[18]	1	185	10%
Cetuximab-FLOX[18]	1	194	16%
Cetuximab-FLOX (intermittent)[18]	1	187	11%
Panitumumab-FOLFIRI[19]	2	1186	<5% difference compared to FOLFIRI
Regorafenib[20]	>1	500	9.6% vs. 5.1% in placebo arm (<5% difference)
Regorafenib[21]	>1	136	2.9% vs. 1.5% in placebo arm (<5% difference)

FLOX= fluorouracil, leucovorin, oxaliplatin;
FOLFIRI= fluorouracil, leucovorin, irinotecan;
FOLFOX-4 = 5-fluorouracil, leucovorin, oxaliplatin;
XELOX= capecitabine, oxaliplatin.
a: Including adjuvant therapy

Clinical Colorectal Cancer, 2016; 16(4): 275-85.

乳癌標靶藥

CDK 4/6 Inhibitor	Neutropenia (%)		Fatigue (%)		Nausea (%)		Diarrhea (%)		QTc prolongation (%)	
	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All
Palbociclib	54	73	2	24	2	16	4	21	NR	NR
Abemaciclib	19	40	2	43	4	57	6	68	NR	NR
Ribociclib	29	46	3	29	2	46	3	22	0	8%

ALK+肺癌標靶藥

Alectinib 600 mg b.i.d. (n = 253)	
Adverse reaction	All grades
Fatigue	41%
Constipation	34%
Edema	30%
Myalgia	29%

Clin Cancer Res; 22(21) November 1, 2016

轉移性腎細胞癌標靶藥疲憊發生率

Review Article

Ongoing Screening and Treatment to Potentially Reduce Tyrosine Kinase Inhibitor-Related Fatigue in Renal Cell Carcinoma

Deepa Anand, MD, and Carmen P. Escalante, MD
Department of General Internal Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

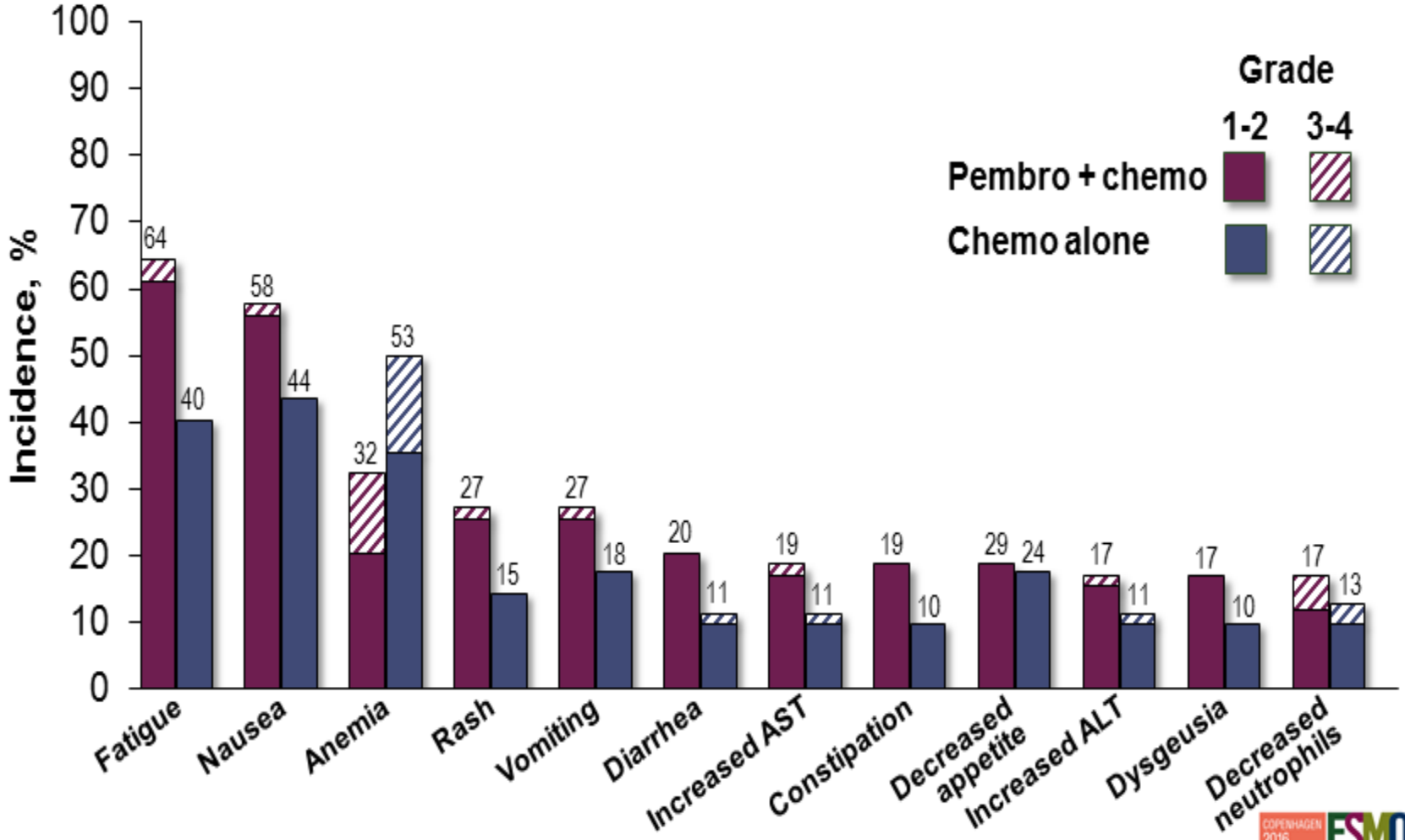
TKI	All-Grade Fatigue (%)	High-Grade Fatigue (Grade 3/4) (%)
Sunitinib	53–81	4–11
Sorafenib	20–43	2–10
Axitinib	39	11
Pazopanib	19–44	2

TKI = tyrosine kinase inhibitor.

J Pain Symptom Manage. 2015 Jul;50(1):108-17

Treatment-Related Adverse Events With Incidence ≥15%

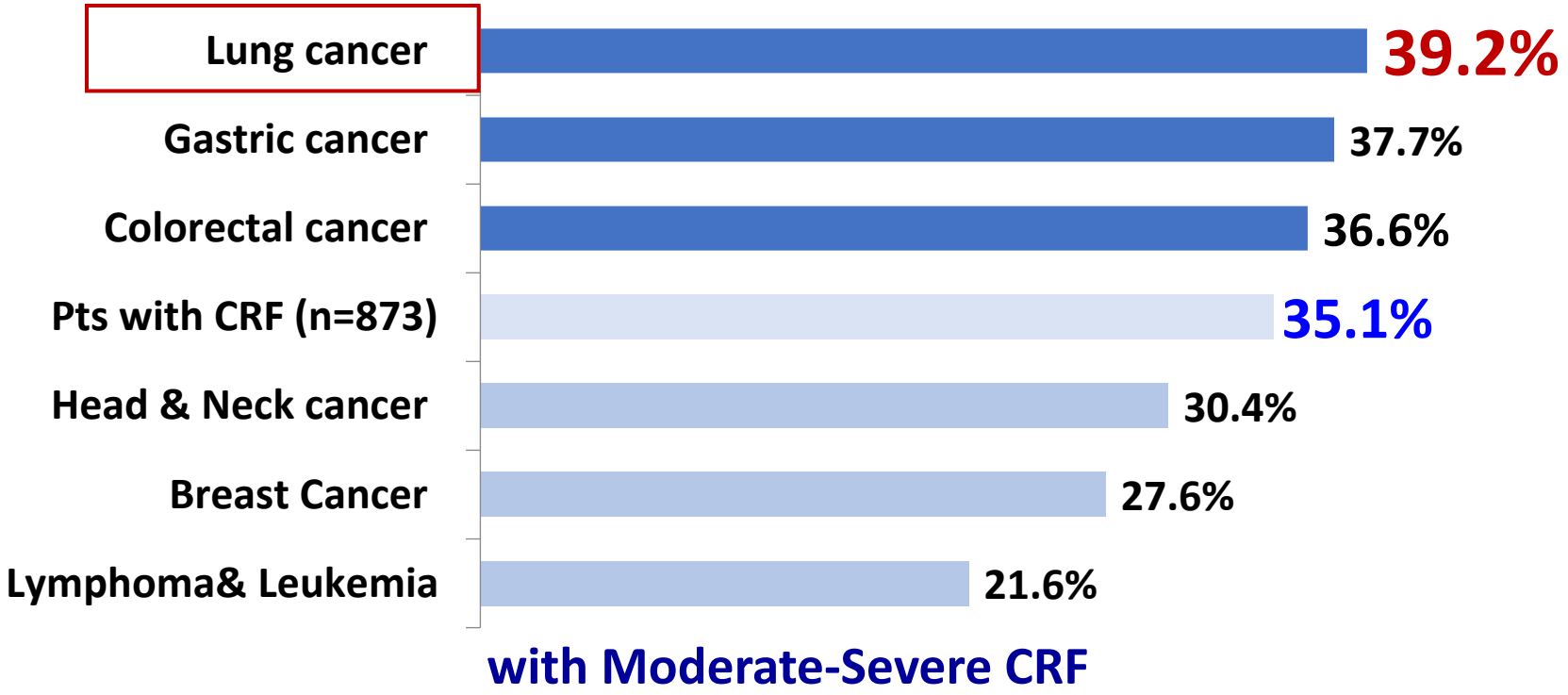
CJ Langer. ESMO 2016.



Data cut-off: August 8, 2016.

有癌因性疲憊的患者，35%為中重度疲憊

肺癌之癌因性疲憊症患者，近40%為中重度疲憊

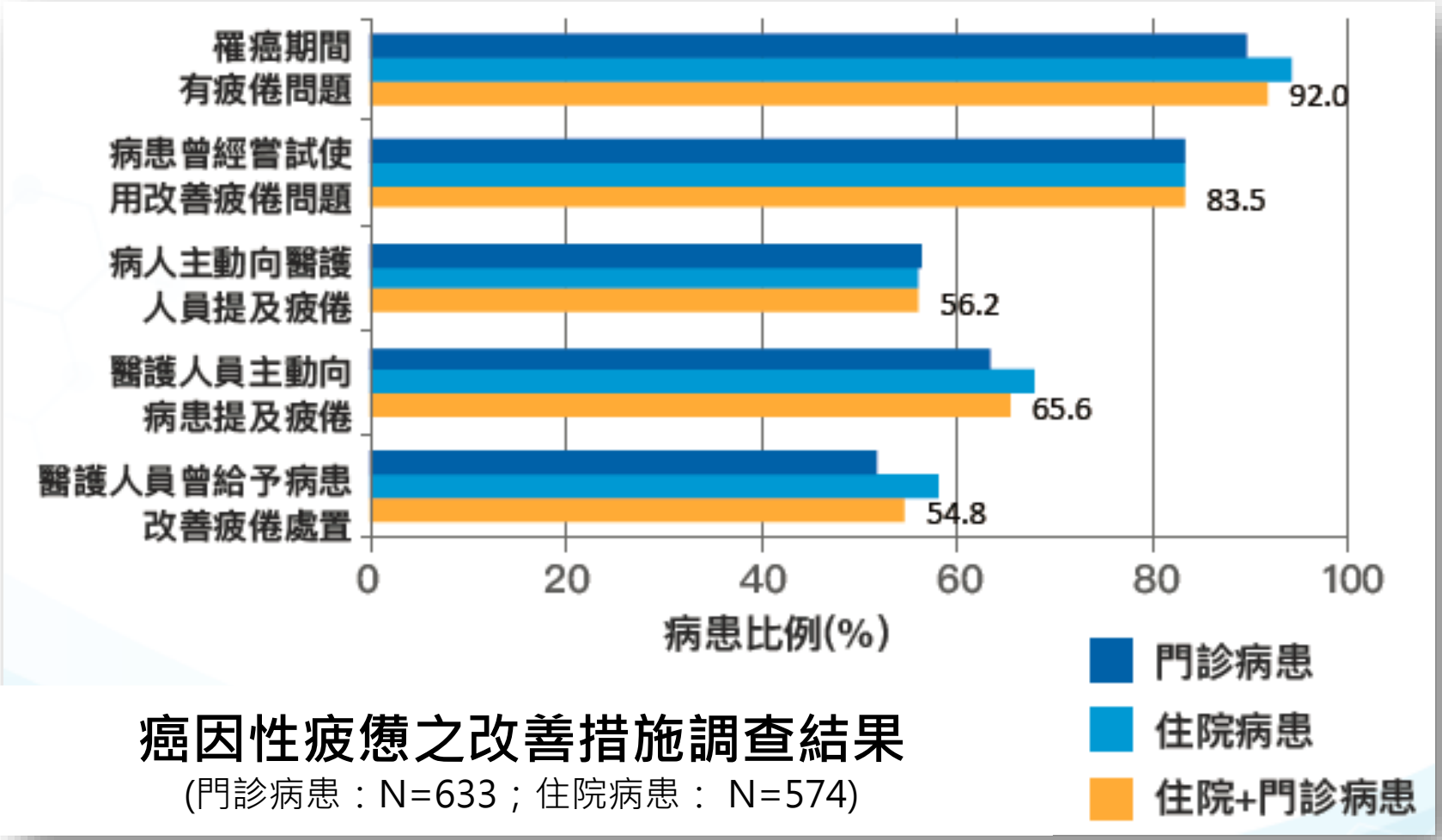


**The severity was calculated from the average of nine items from BFI –T and categorized into mild (<4), moderate (4-6.99), Severe (≧7).*

K. M. Rau et. Al., Japanese Journal of Clinical Oncology, 2020, 1–9

2015 Palliative Care in Oncology Symposium, Boston; Oct 9-10, 2015, Abstract # 155471. 2016 MASCC Poster # MASCC-0488.

92% 台灣癌症患者罹癌期間有疲憊問題，約一半癌症病患主動向醫護人員提及疲憊



癌因性疲憊之改善措施調查結果

(門診病患：N=633；住院病患： N=574)

K. M. Rau et. Al., Japanese Journal of Clinical Oncology, 2020, 1–9.

2015 Palliative Care in Oncology Symposium, Boston; Abstract # 155471. 2016 MASCC Poster # MASCC-0488.

癌因性疲憊症之臨床治療指引

MANAGEMENT OF CANCER-RELATED FATIGUE – A GUIDELINE FOR TAIWAN –

2017年 11月 第一版

台灣癌症安寧緩和醫學會

台灣腫瘤護理學會

癌因性疲憊評估與治療

以NRS或BFI-T評估疲憊

<4分 輕度疲憊

非藥物治療

運動、營養飲食、認知行為治療、睡眠衛生等

≥4分 中重度疲憊

加上藥物治療

- 癌因性疲憊適應症處方用藥
  PG2 Injection
- 其他用藥
  類固醇、中樞神經興奮劑

癌因性疲憊症之藥物治療

黃耆多醣注射劑有初步臨床試驗顯示可改善中重度癌因性疲憊症。 (Level IA, Grade A)	**蔘類**在臨床試驗顯示可以改善癌因性疲憊，但因中藥在使用上會因原料製備等影響，建議使用前應諮詢醫療團隊。 (Level IB, Grade B)
Methylphenidate 臨床研究顯示使用於疲憊程度或病情較嚴重的病人較具效果；但在用藥前應審慎考量劑量、用藥時間、濫用風險、及病人個人疾病等臨床情形，充分評估相關風險與效益。 (Level IA, Grade A)	**Methylprednisolone、dexamethasone**等類固醇藥物有臨床證據顯示可以改善癌症病人的疲憊和生活品質，但長期使用有安全風險，故建議只用於癌症末期、合併疲憊與厭食症、或有腦部或骨骼轉移而疼痛的癌症病人。 (Level IB, Grade B)

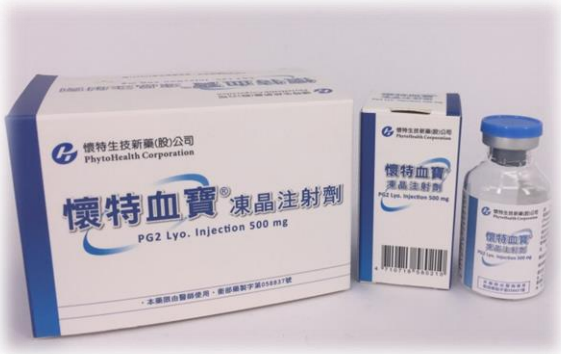
癌因性疲憊治療適應症之處方用藥
PG2® Injection

- 成份：黃耆多醣 (Polysaccharides of *Astragalus membranaceus*)
  萃取物 500 mg ，不含任何賦形劑。
  分子量約20,000~60,000 Da

- 適應症：**適用於癌症末期因疾病進展所導致中重度疲勞症狀之改善**

- 機轉：增強免疫功能及刺激骨髓造血功能

- 用法及用量：
  - 成人每次劑量 500 mg，
    以 2.5 - 3.5 小時點滴靜脈滴注。
  - 每週2 - 4次，使用2 - 4週。



食品藥物管理署(TFDA)核准之第一個植物性處方用藥：衛部藥製字第058837號

健保好康報

乳癌 癌因性疲憊症 新希望~

「懷特血寶」(PG2 黃耆多醣萃取物)
從3月1日起~ 健保給付囉!!

給付條件：

限第四期，因疾病進展致中重度疲憊之乳癌病人:

1 疲憊分數 ≧4 (BFI-T或VAS)，且經其他處置無效，體能狀態佳 (ECOG 0~2)的中、重度癌因性疲憊症。

2.不含住院安寧療護者。

3. 每位病人終生給付6支為上限。

*須經「事前審查」核准後使用。 *以上僅為給付原則，詳細條件請您諮詢醫師喔!

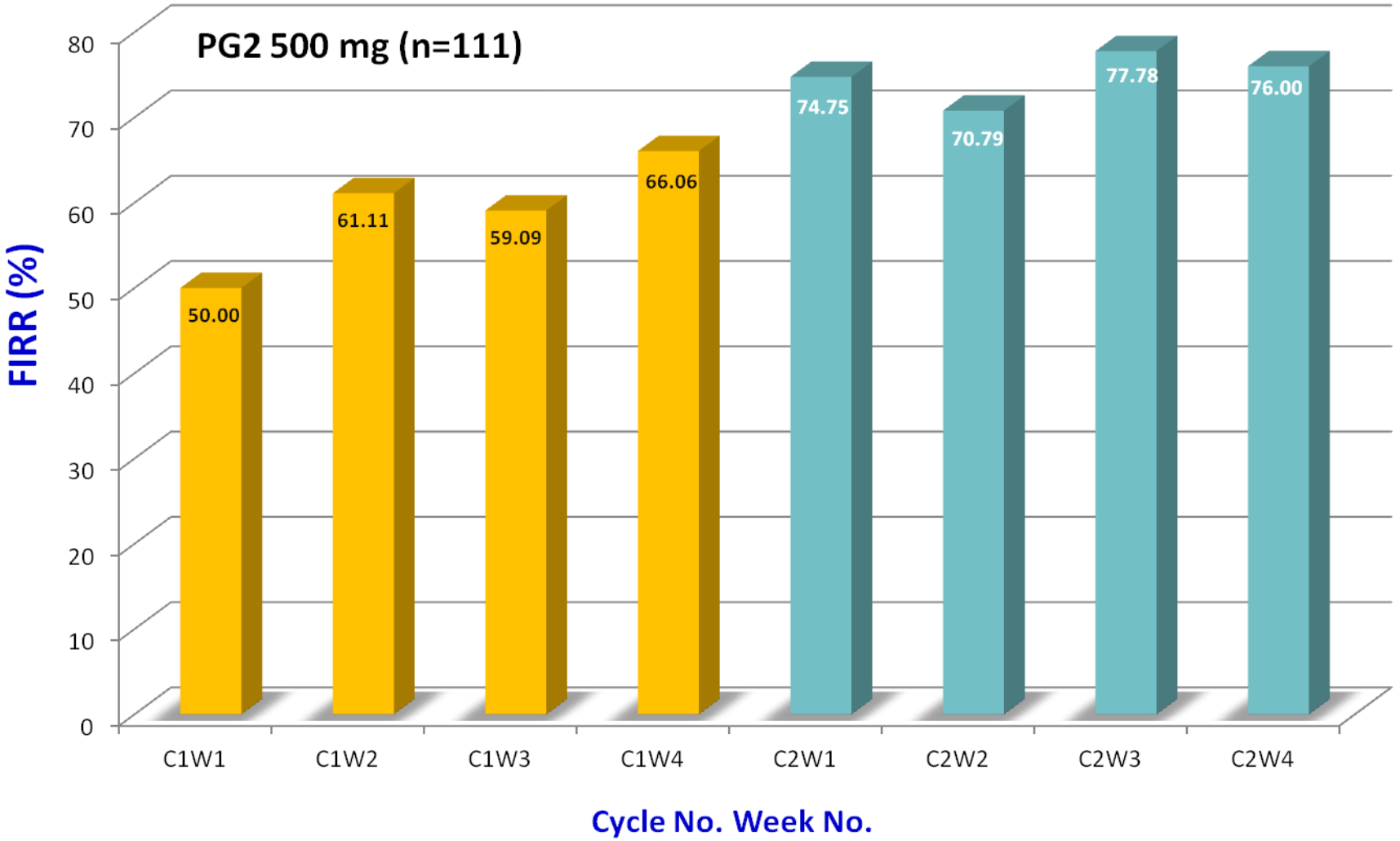
HOPE 財團法人癌症希望基金會 HOPE FOUNDATION for CANCER CARE

PG2 Phase IV Trial

Center	馬偕，雙和，基隆長庚情人湖院區，三總，彰基，奇美柳營，中醫大，林口長庚，高雄長庚
Trial Objective	To evaluate the **efficacy and safety** of different doses of PG2 for relieving fatigue among advanced cancer patients who are under standard palliative care (SPC).
Blinding/ Randomization	Double-blinded/Randomized
Population	Advanced progressive cancer patients with moderate to severe fatigue (**BFI Fatigue score ≥ 4**) under palliative care.
Treatment Regimens	Two parallel arms: (1:1 ratio) 1. PG2 500 mg by IV infusion for 3 days per week 2. PG2 250 mg by IV infusion for 3 days per week
Study Period	8 weeks
Primary Endpoint	Fatigue Improvement Response Rate (FIRR)
Sample Size	Enrolled Patient No.: 323 Evaluable Patient No.: 214

FIRR by Week during the Whole Study Period

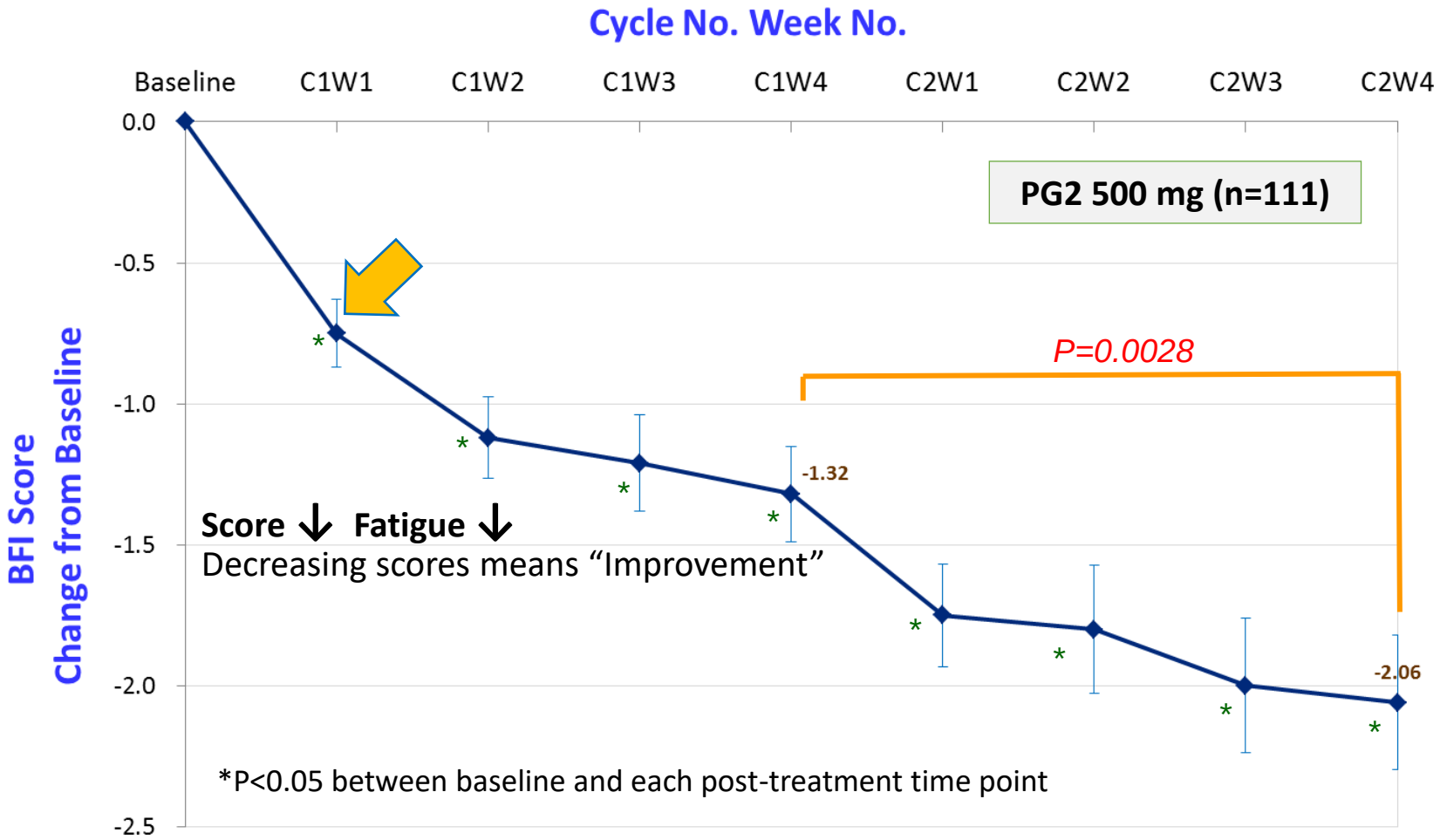
*Cut-off Point of FIR: 10 %**



*** Fatigue Improvement Responder (FIR): Clinically effective (Brief Fatigue Inventory, BFI) ≥10% Improvement from baseline.**

J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. PhytoHealth In-house Data

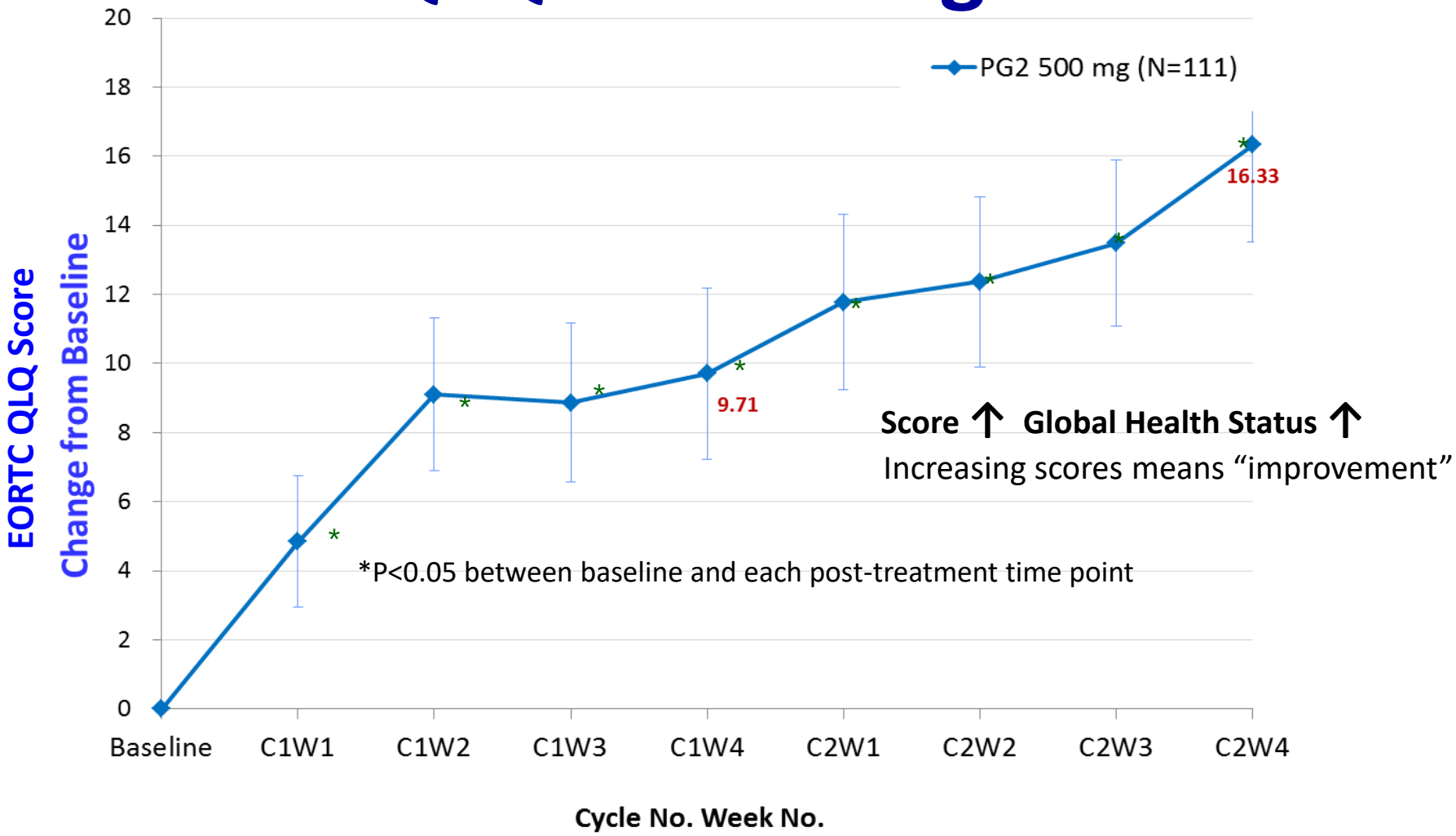
Mean BFI Score Change



- ✓ **PG2 treatment showed efficacy in relieving fatigue as early as the first week of treatment.**
- ✓ **PG2 is more effective at the end of cycle 2 compared to cycle 1.**

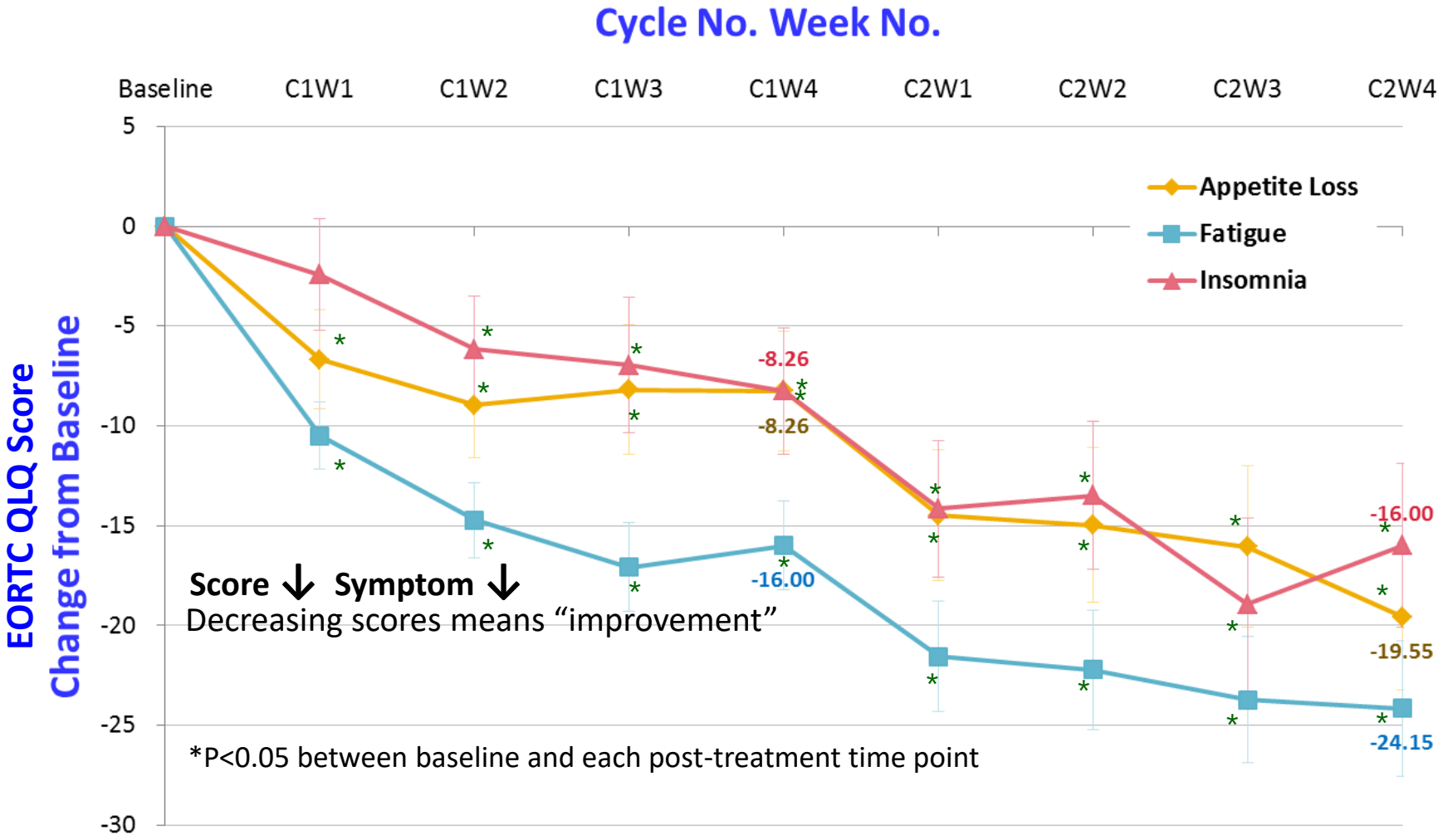
J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091.

Global Health Status: EORTC-QLQ-C30 Change



2018 MASCC e-Poster Presentation; J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. PhytoHealth In-house Data

Global Health Status: domains with significant improvement



2018 MASCC e-Poster Presentation; J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. PhytoHealth In-house Data

cancers

MDPI

Article

Karnofsky Performance Status as A Predictive Factor for Cancer-Related Fatigue Treatment with Astragalus Polysaccharides (PG2) Injection—A Double Blind, Multi-Center, Randomized Phase IV Study

Cheng-Hsu Wang [1], Cheng-Yao Lin [2], Jen-Shi Chen [3,4], Ching-Liang Ho [5], Kun-Ming Rau [6,7,8], Jo-Ting Tsai [9,10], Cheng-Shyong Chang [11], Su-Peng Yeh [12], Chieh-Fang Cheng [13] and Yuen-Liang Lai [14,15,*]

Received: 22 October 2018; Accepted: 15 January 2019; Published: 22 January 2019

check for updates

Cancers **2019**, *11*, 128; doi:10.3390/cancers11020128

www.mdpi.com/journal/cancers

Cancers . 2019 Jan 22;11(2):128-140.

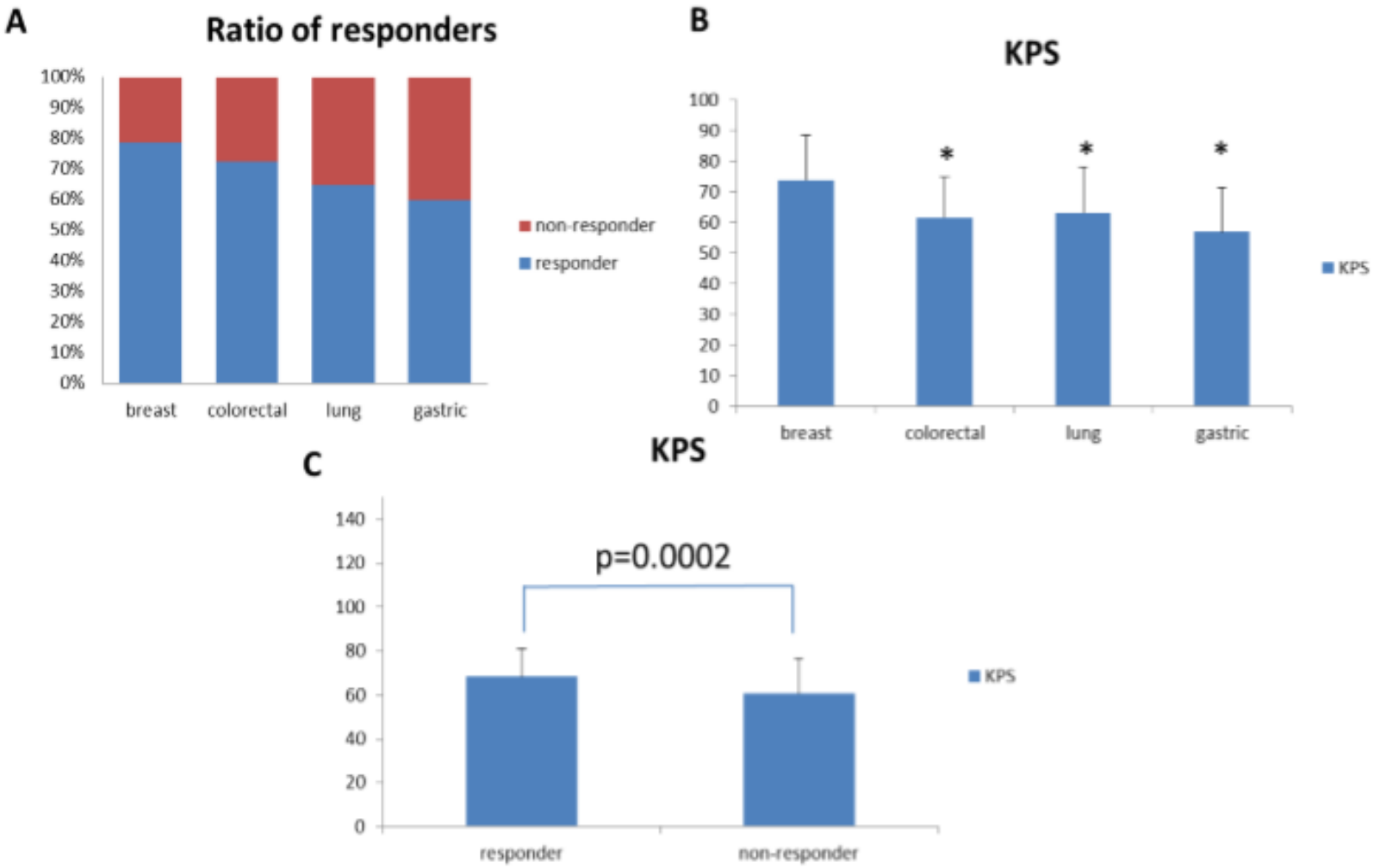


Figure 3. Fatigue Improvement Response Rate and KPS for patients with different cancer types. (**A**) Breast, colon, lung, and gastric cancer patients were selected for analysis. Fatigue improvement response rates for these patients were analyzed and compared. (**B**) KPS for breast, colon, lung, and gastric cancer patients were analyzed and compared. (**C**) KPS for responders and non-responders in the overall patient population. (* $p < 0.01$ versus breast cancer patients).

Cancers. 2019 Jan 22;11(2): 128-140.

Multivariate analysis for responders and non-responders to PG2

- Patients with **higher KPS** responded **better to PG2**.
- Identified **KPS as a promising predictive factor** for the therapeutic efficacy of PG2.

Table 3. Multivariate analysis for responders and non-responders to Astragalus Polysaccharides (PG2) injection.

	Cut-off Points = 10%			Multivariate Analysis	
Variable/Status	**Responder (N = 140)**	**Non-Responder (N = 74)**	**Univariate Analysis p-value ***	**Odds Ratio (95% CI)**	***p*-value ****
Baseline KPS score					
30–50	22 (15.71%)	31 (41.89%)	<0.0001 C	0.253 (0.126, 0.504)	<0.0001
60–90	118 (84.29%)	43 (58.11%)			

All Subjects					
4–6	72 (51.43%)	41 (55.41%)	0.5794 C	0.885 (0.475, 1.647)	0.6998
7–10	68 (48.57%)	33 (44.59%)			
Cancer Type: three categories					
Lung cancer	22 (15.71%)	12 (16.22%)	0.2876 C		
Breast cancer	22 (15.71%)	6 (8.11%)		1.297 (0.343, 4.905)	0.7020
other	96 (68.57%)	56 (75.68%)		0.957 (0.414, 2.208)	0.9173
Albumin (g/dL)					
<3.0	20 (14.29%)	11 (14.86%)	0.9088 C	1.272 (0.518, 3.124)	0.5997
≥3.0	120 (85.71%)	63 (85.14%)			
Hemoglobin (g/dL)					
<10	48 (34.29%)	30 (40.54%)	0.3659 C	0.767 (0.405, 1.452)	0.4148
≥10	92 (65.71%)	44 (59.46%)			
Peripheral blood TLC (/μL)					
<700	46 (32.86%)	18 (24.32%)	0.1947 C	1.709 (0.846, 3.452)	0.1353
≥700	94 (67.14%)	56 (75.68%)			

* The Wilcoxon rank-sum test W was used to compare the difference between responders and non-responders for continuous variables; the Chi-squared test C was used to compare the difference between responders and non-responders for categorical variables. ** A logistic regression model was used to compare the differences between responders and non-responders.

Baseline KPS score	Responder %
30-50 (N=53)	22 (42%)
60-90 (N=161)	118 (73%)

Cancers. 2019 Jan 22;11(2): 128-140.

Summary of PG2® Phase IV Study

- **Fatigue improvement**

✓ PG2® treatment showed efficacy in relieving fatigue as early as the first week of treatment.

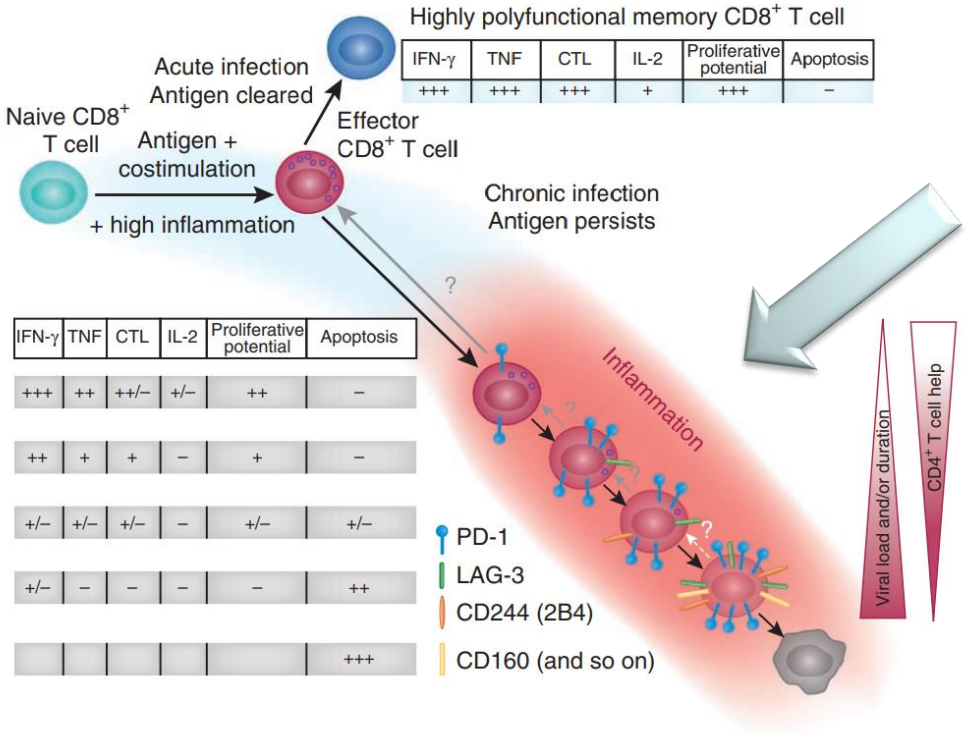
✓ Clinically meaningful fatigue improvement (≥ 10%) was observed in more than 65% of subjects receiving PG2® after the cycle 1 treatment when compared to baseline.

✓ Patients with higher KPS showed better chance to respond to PG2 treatment in BFI-T score.

J Clin Oncol 36, 2018 (suppl; abstr 10091); 2018 ASCO Annual Meeting, Poster Presentation Abstract #: 10091. Cancers. 2019 Jan 22;11(2): 128-140.

T cell exhaustion in chronic infection and cancer

- **T cell exhaustion is a state of T cell dysfunction that arises during many chronic infections and cancer.**
  - **Resulted poor effector function, sustained expression of inhibitory receptors**
  - **Prevents optimal control of infection and tumors**



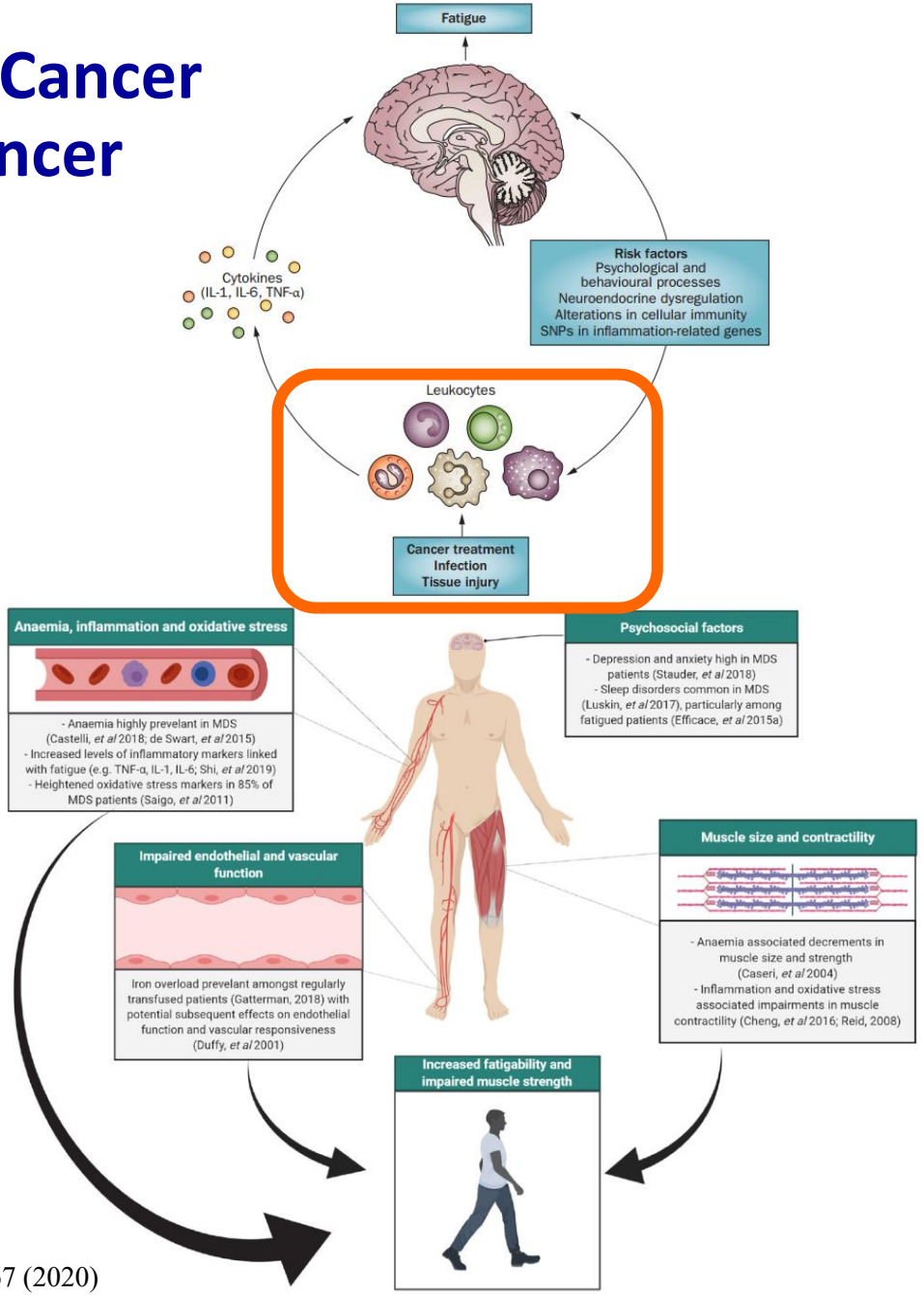
During chronic infection (bottom), infection persists after the effector phase. As antigen and/or viral load increases, T cells progress through stages of dysfunction, losing effector functions and other properties in a hierarchical manner

The severity of T cell exhaustion is correlated with increasing inhibitory receptor expression, high viral (or antigen) load, loss of CD4+ T cell help and prolonged infection

Wherry. Nat. Immun., 2011, 12(6):492-9

Physiological Effects of Cancer and its Impact on Cancer Related Fatigue

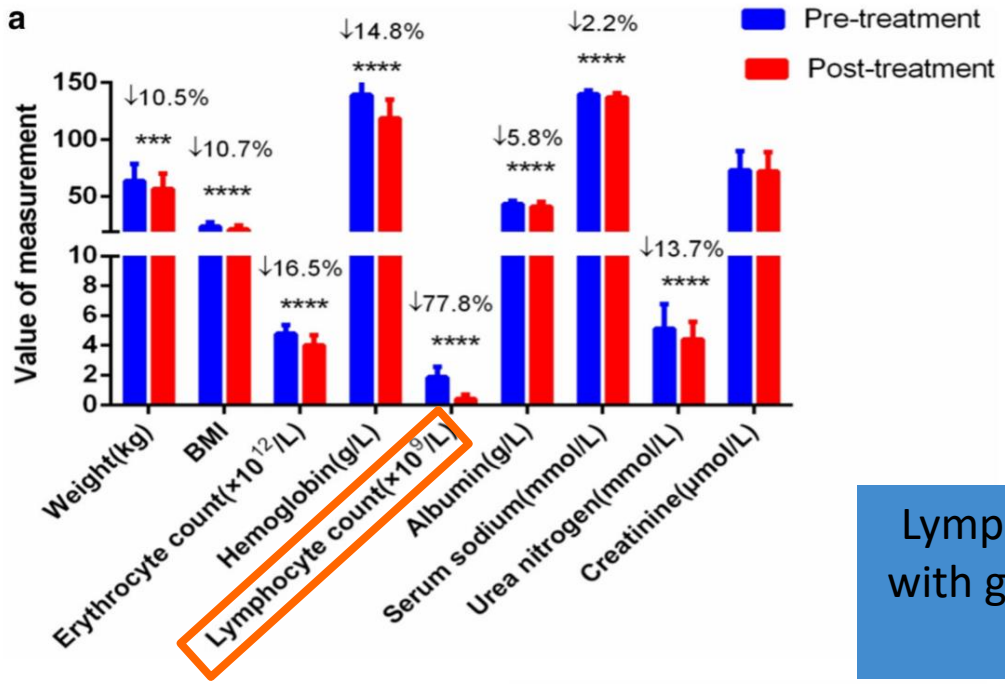
- Chronic inflammation
- Oxidative stress
- Impaired endothelial and vascular function
- Deconditioning in muscle size and contractility



Bower, J. E. *Nat. Rev. Clin. Oncol.* **11**, 597–609 (2014).

Brownstein, C. G., et al. *Crit. Rev. Oncol. Hematol.* **154**, 103067 (2020)

Lymphocyte count was negatively correlated with fatigue



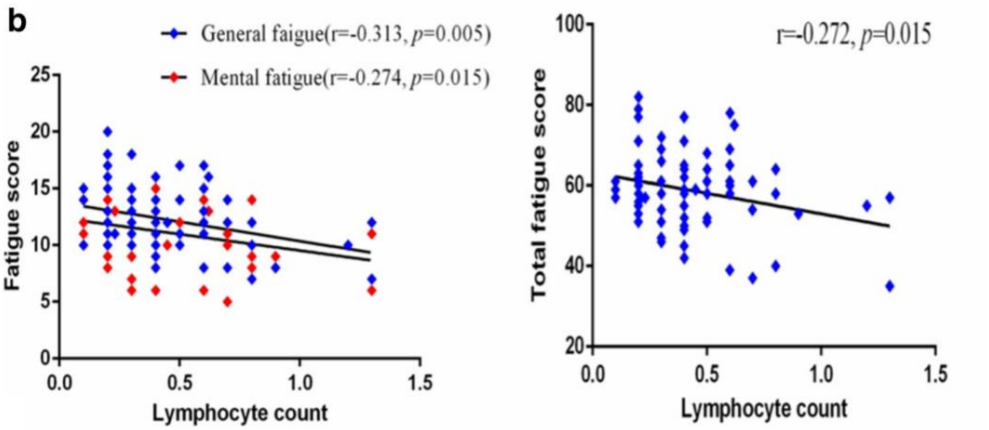
Supportive Care in Cancer
https://doi.org/10.1007/s00520-021-06054-7

ORIGINAL ARTICLE

Multidimensional fatigue in patients with nasopharyngeal carcinoma receiving concurrent chemoradiotherapy: incidence, severity, and risk factors

Lin-Min Chen[1,2] · Qiu-Lan Yang[1,2] · Yu-Yu Duan[1,2] · Xue-Zhen Huan[1,2] · Yan He[1,2] · Cong Wang[1,2] · Yu-Ying Fan[1,2] · Yu-Cong Cai[1,2] · Jian-Mei Li[1,2] · Li-Ping Chen[1,2] · Hui-Ying Qin[1,3]

Received: 10 November 2020 / Accepted: 7 February 2021



Lymphocyte count was negatively correlated with general fatigue, mental fatigue, and total fatigue.

(Observations)

Lowered both effector and regulatory immune cells in fatigued patients

(Inductive reasoning)

https://doi.org/10.1007/s00520-021-06054-7

PG2: Lung Cancer Patients with IO Therapy

High NLR was associated with a poor response and decreased survival → Examine whether PG2 might **normalize the NLR** and affect the overall survival of patients with lung cancer treated with immunotherapy.

Site	Chung Shan Medical University Hospital
Collection Period	2015/10~2019/11
IO Therapy	IO combined with chemo and /or TKI
Groups	1) **PG2 group**: PG2 combined with IO Therapy 2) **Control group**: IO Therapy alone
Study Timepoints	Baseline：within 3 days prior to initiation of IO 6^{th} week： 6 ± 2 weeks after baseline
Primary Endpoint	NLR change (**all patients, baseline NLR ≥5 and <5**) • **Decrease or no change**: The NLR decreased or increased <25% from baseline. • **Increase**: The NLR increased ≥ 25% from baseline.

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

Distribution of the change in the NLR 6 weeks after ICI initiation

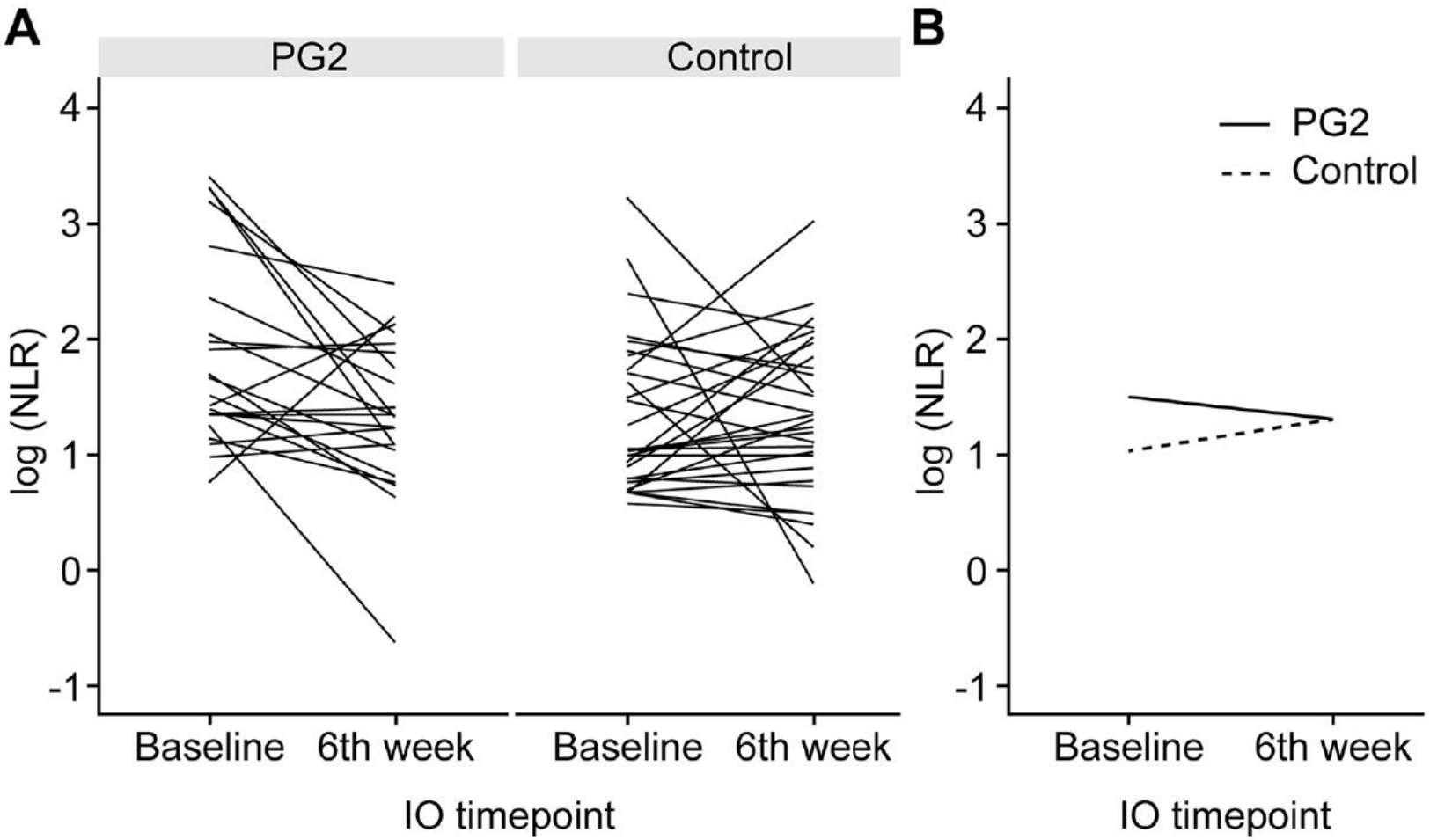
Patients with lung cancer who received combination therapy with PG2 and ICIs had a stable or decreased NLR 6 weeks after treatment initiation

PG2 組維持NLR穩定的人數比例顯著高於Control 組

Population	Classification	PG2		Control		p value‡
		N	(%)	N	(%)	
All Patients N = 53	Decrease or no change*	21	(91.3%)	19	(63.3%)	0.028
	Increase†	2	(8.7%)	11	(36.7%)	
Baseline NLR ≥5 N = 21	Decrease or no change*	11	(100%)	8	(80.0%)	0.214
	Increase†	0	(0%)	2	(20.0%)	
Baseline NLR <5 N = 32	Decrease or no change*	10	(83.3%)	12	(60.0%)	0.139
	Increase†	2	(16.7%)	8	(40.0%)	

Abbreviations: ICI: immune checkpoint inhibitors; NLR, neutrophil to lymphocyte ratio
*Decrease or no change: The NLR decreased or increased <25% from baseline.
†Increase: The NLR increased 25% from baseline.
‡Chi-square test or Fisher Exact test

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

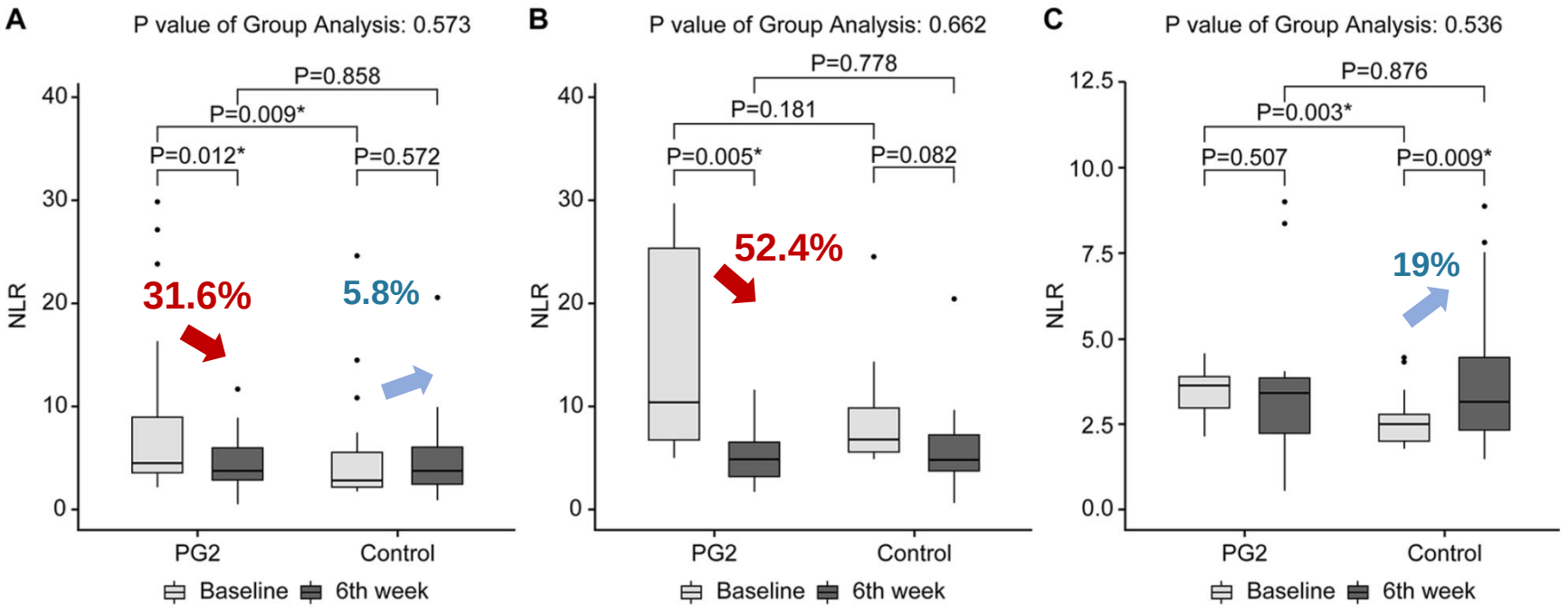


Change in the NLR before and 6 weeks after ICI initiation among all patients.
(A) Each line represents the data for an individual patient.
(B) The **median** of the 2 groups.

Abbrev. ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio.

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

NLR at baseline and 6 after ICI initiation



(A) All patients. (B) Patients with a baseline NLR ≥ 5. (C) Patients with a baseline NLR <5.

(Mann–Whitney tests: *P < .05.)

(A) The NLR value of the PG2 group at the 6th week was significantly decreased from baseline (-1.92, p = 0.012), while that of control group was slightly increased from baseline (0.13, 5.8%).

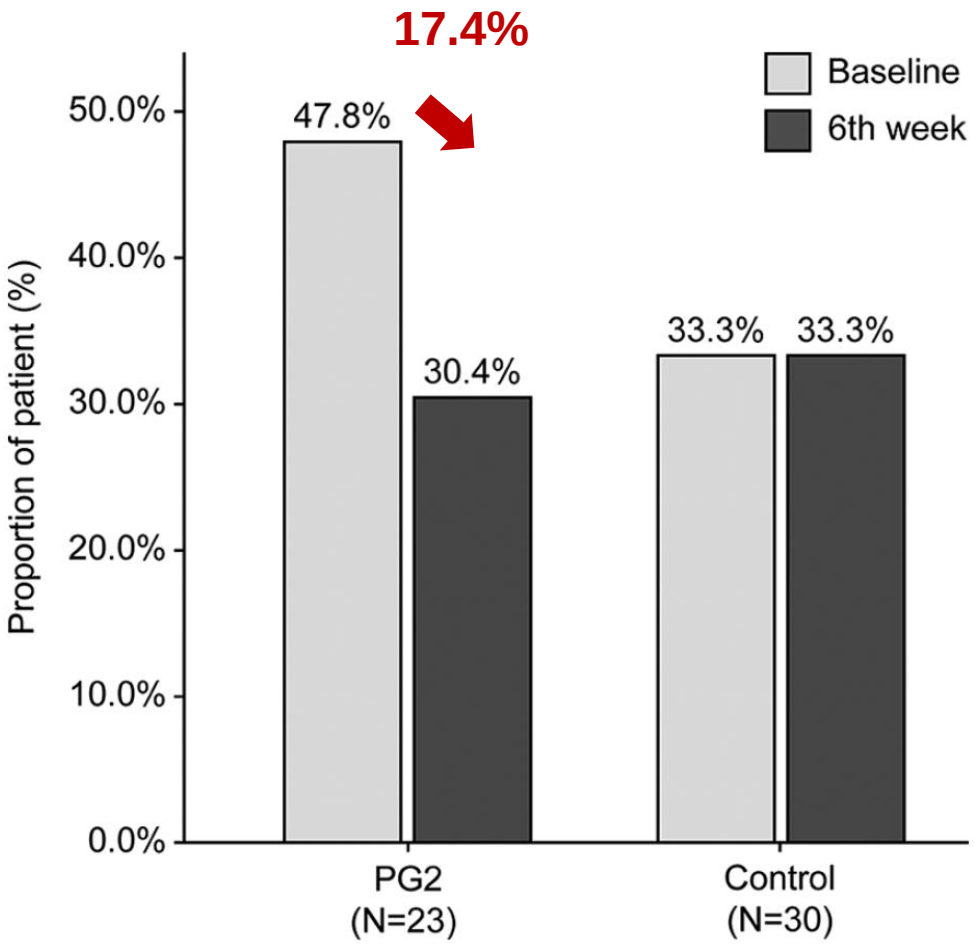
(B) In the subgroup of baseline NLR≧5, the NLR values had a statistically significant decrease in the PG2 group (-4.8, p=0.005), but had no significant change in the control group after 6 weeks of ICIs treatment.

(C) The NLR values had slightly increased in the PG2 group (P=0.507) , but notably increased by 19% after 6 weeks of treatment in the control group (0.52, p=0.009).

Abbrev. ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio.

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

The proportion of patients with an NLR ≥ 5 at baseline and 6 after initiation of ICIs

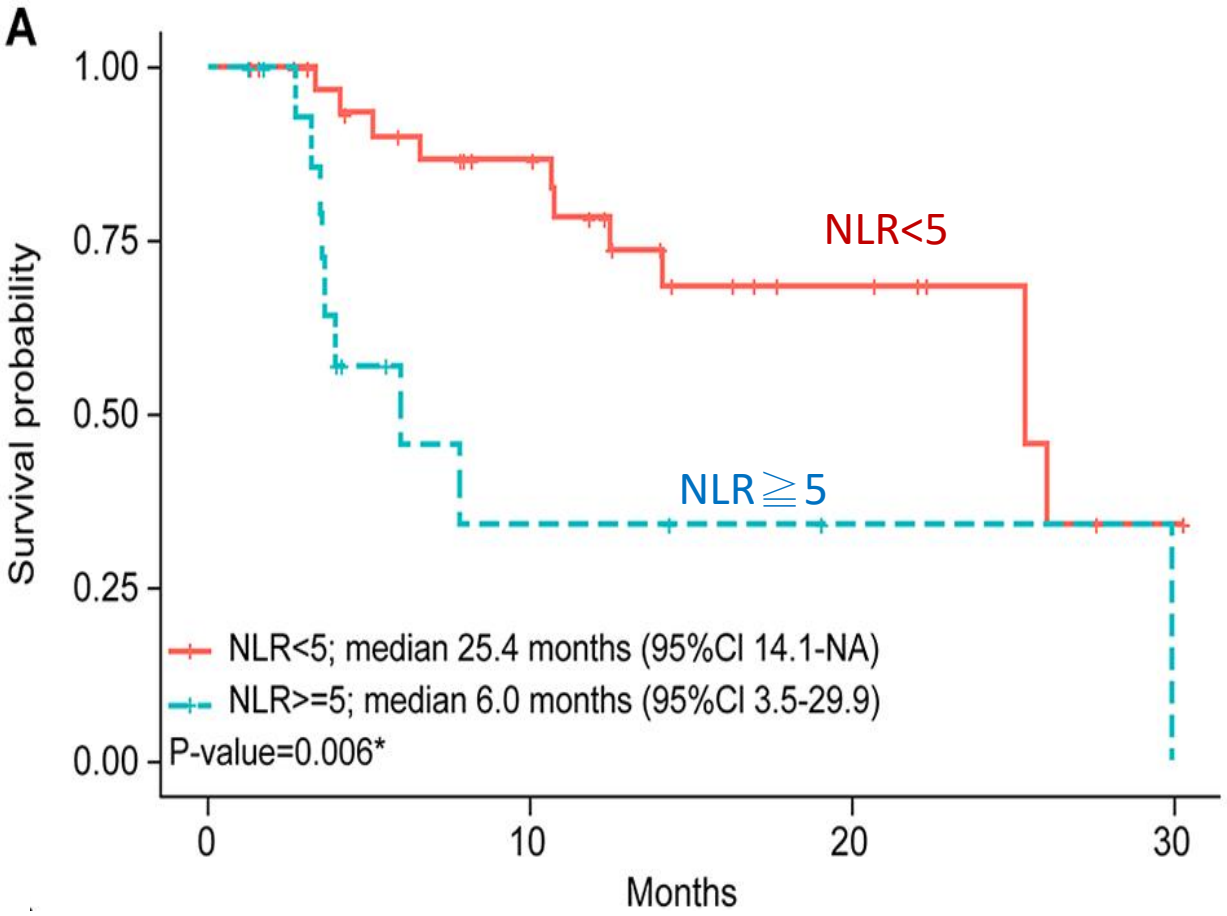


The proportion of patients with NLR≧5 was decreased by 17.4% in the PG2 group and no change in the control group after ICIs treatment.

Abbrev. ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio.

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

Overall survival：Patients with a baseline NLR ≥5 vs. <5.



Patients with a high NLR (≥ 5) at 6 weeks had a significantly shorter OS than those with a low NLR (<5) (*p=0.009)*.

As PG2 stabilizes or decreases the NLR, might promote the antitumor immune effect created by immunotherapy and then prolong survival.

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

PG2 could normalize the NLR in patients with lung cancer receiving ICI combination treatments

"Decrease or no change" in the NLR (% of patient)	
PG2 group	**91.3% (P = .028 vs. control group)**
Control group	63.3%

NLR vs. baseline	
PG2 group	**decreased by 31.60% (P = .012)**
Control group	increased by 5.80% (P = .572)

Overall survival (both groups had a median NLR of 3.73)	
PG2 group	26.1 months
Control group	25.4 months

PG2 group had a higher median baseline NLR than the control group (PG2 vs Control, 4.51 vs 2.81, respectively).

Ref. Integr Cancer Ther. Jan-Dec 2021;20:1534735421995256. doi: 10.1177/1534735421995256.

nutrients

MDPI

Article

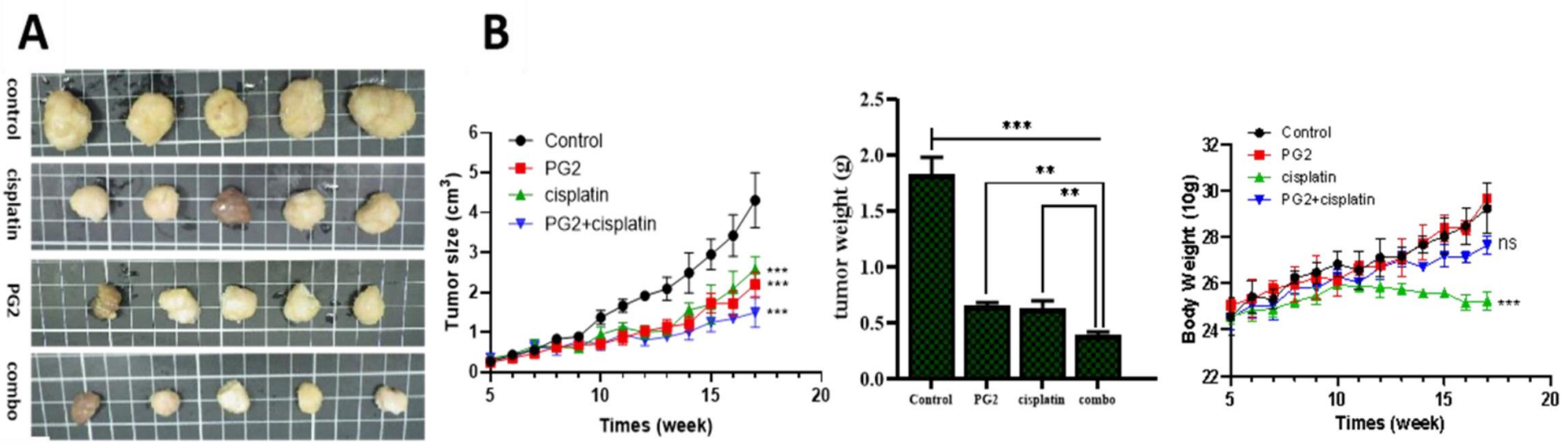
Astragalus polysaccharides (PG2) Enhances the M1 Polarization of Macrophages, Functional Maturation of Dendritic Cells, and T Cell-Mediated Anticancer Immune Responses in Patients with Lung Cancer

Oluwaseun Adebayo Bamodu [1,2,†], Kuang-Tai Kuo [3,4,†], Chun-Hua Wang [5,6], Wen-Chien Huang [7,8], Alexander T.H. Wu [9], Jo-Ting Tsai [10,11], Kang-Yun Lee [12], Chi-Tai Yeh [1,2,13,*] and Liang-Shun Wang [3,4,*]

1 Division of Hematology & Oncology, Department of Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City 235, Taiwan; 16625@s.tmu.edu.tw
2 Department of Medical Research and Education, Shuang Ho Hospital, Taipei Medical University, New Taipei City 235, Taiwan
3 Division of Thoracic Surgery, Department of Surgery, Shuang Ho Hospital, Taipei Medical University, New Taipei City 235, Taiwan; doc2738h@gmail.com
4 Division of Thoracic Surgery, Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei City 110, Taiwan

Nutrients_2019(11)2264-2283.

Inhibited tumor growth & suppressed cisplatin-associated weight-loss



(A) Photo images show the anticancer effect of cisplatin and/or PG2 in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

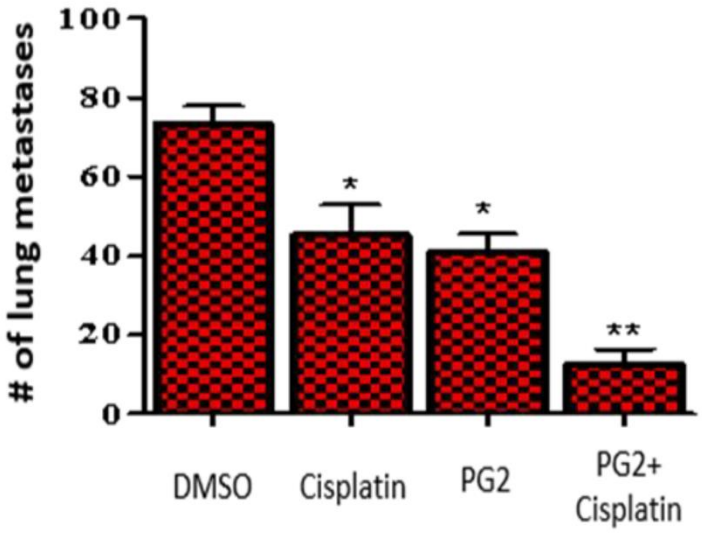
(B) Graphical representation of the effect of cisplatin and/or PG2 on the tumore size, tumor weight, and body weight in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

*ns, not significant; **p < 0.01, ***p < 0.001;*

(17 weeks, and/or cisplatin in syngeneic LLC1 tumor-bearing C57BL/6 mice)

Nutrients_2019(11)2264-2283.

Suppression of tumor growth and metastasis



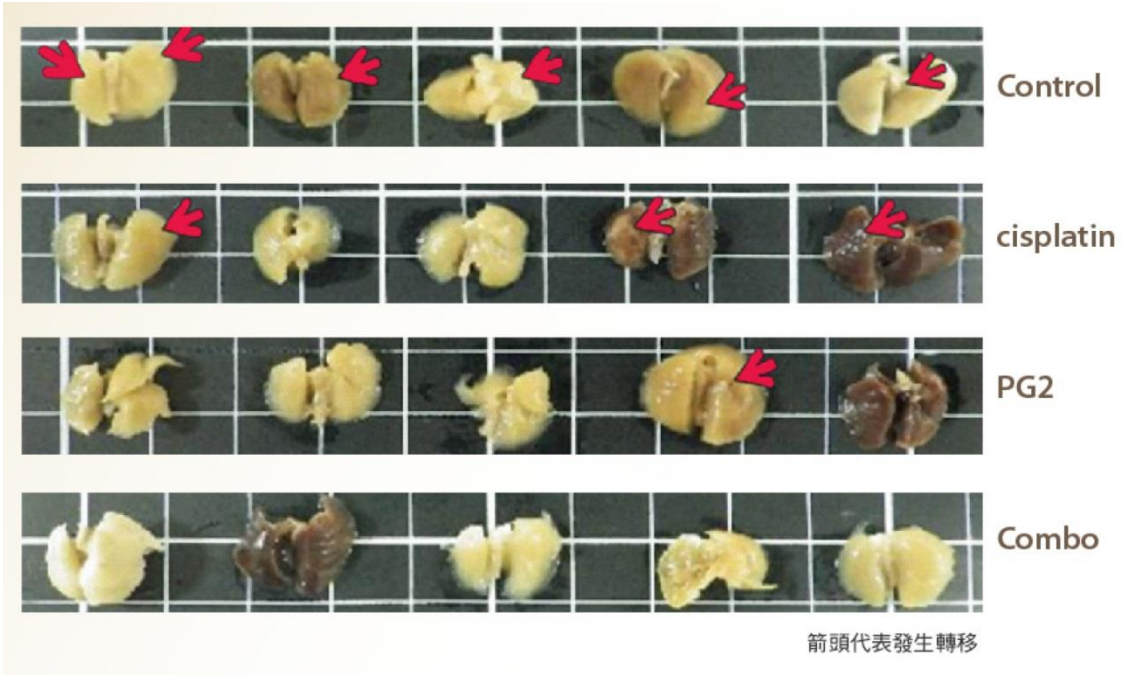


Photo images show the effect of cisplatin and/or PG2 on metastasis in syngeneic C57BL/6 mice inoculated with 1.5x103 LLC1 cells.

*ns, not significant; *p < 0.05, **p < 0.01; DMSO, dimethyl sulfoxide*

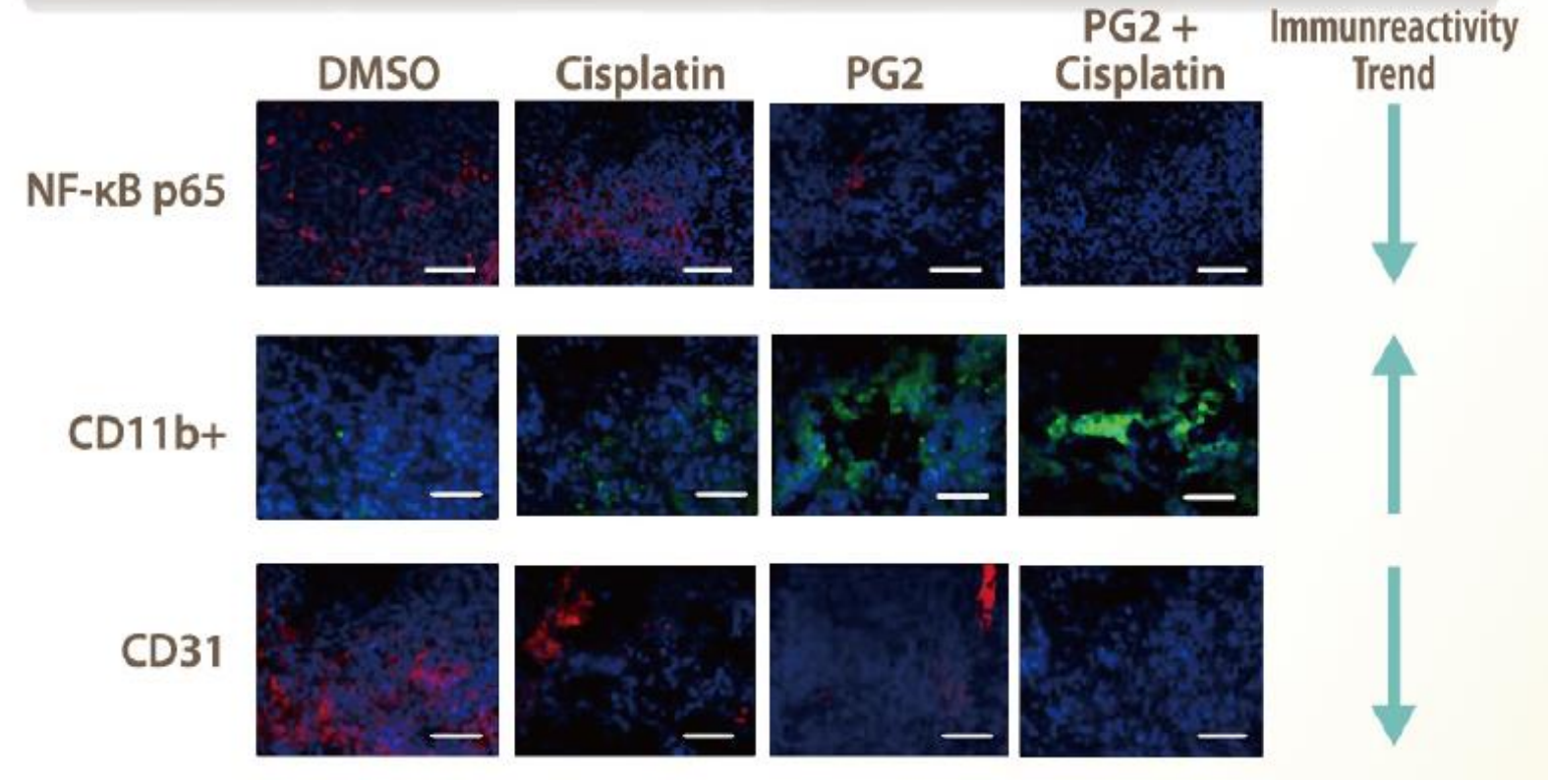
(17 weeks, and/or cisplatin in syngeneic LLC1 tumor-bearing C57BL/6 mice)

Nutrients_2019(11)2264-2283.

U.S. Patent. Patent No.: US 10,478,468 B2. Method for enhancing effect of immunotherapy for cancer

Regulating tumor micro-environment & suppressing tumorigenicity

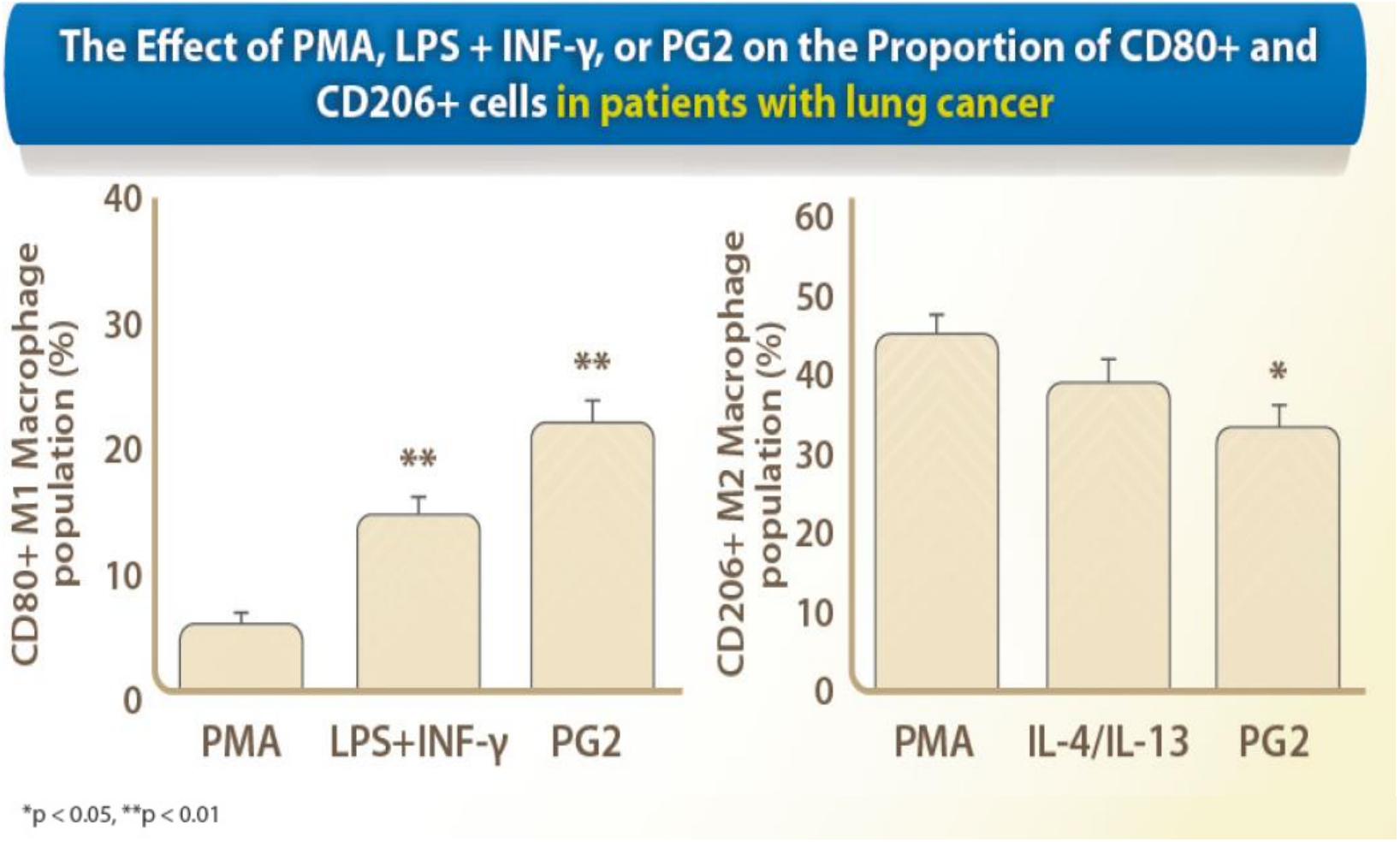
Immunofluorescent staining showed that PG2 or cisplatin can reduced the expression of beta subunit (NF-κB), CD11b, and CD31 in C57BL/6 mice



Nutrients_2019(11)2264-2283.

U.S. Patent. Patent No.: US 10,478,468 B2. Method for enhancing effect of immunotherapy for cancer

Regulating tumor micro-environment & suppressing tumorigenicity



Nutrients_2019(11)2264-2283.

PG2®: beyond Cancer-related Fatigue Treatment

- **A therapeutically-relevant role for PG2 in modulating the M1/M2**
  - ✓ The treatment with PG2 elicited significant depletion of the tumor-associated M2 population.
- **Synergistically enhanced the anticancer effect of chemotherapeutic agent, cisplatin**
  - ✓ Inhibited tumor growth and metastasis.
  - ✓ In the presence of PG2, cisplatin-associated cachexia and weight-loss was markedly suppressed.

Nutrients_2019(11)2264-2283.

幫助病患改善癌因性疲憊

- 92% 台灣癌症患者罹癌期間有疲憊問題，1/4 癌症病患有中重度疲憊
  - ✓ 癌因性疲憊症之ICD-10 code：**R53.0**
- 癌症病患應在初診和回診時，接受規律性疲憊評估
  - ✓ 住院患者為每日評估，門診患者則每次回診時評估
- 癌症病患依疲憊嚴重程度給予相對應的治療，治療後再評估疲憊程度
  - ✓ 輕度：非藥物治療，**VAS≧4**中重度：加上藥物治療
- 台灣癌因性疲憊症臨床指引建議：中度以上癌因性疲憊症之具適應症藥物為黃耆多醣注射劑(PG2)。
- 合併使用黃耆多醣注射劑(PG2)，可改善癌症患者之疲憊症，使癌症療程能順利完成。

癌因性疲憊症規律評估

以0分為沒有疲憊，10分為想像中最嚴重的疲憊，請您根據自身疲憊的感覺指出對應的疲憊分數。或選擇最能代表您疲備狀態的圖像及其對應的分數。

疲憊日誌

每天規律的評估、記錄疲憊分數或處置方法，這些資料有助您的醫療團隊更有效的提供處置方案。

		非藥物處置	藥物處置
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____
日期 疲憊分數		□運動 □睡眠衛生 □輔助治療 □心理社會措施 □營養處置 □其他____	□精神刺激藥物 □類固醇 □黃耆多醣注射劑 □中草藥藥物 □其他____

♥ 貼心小叮嚀 ♥

遵照醫護人員的指示，配合治療方式調整生活，按時複診，如果藥物的幫助不大，或是有副作用，請告訴醫護人員。請記住，您的疲憊是可以緩解的！

疲憊量尺

根據臺灣癌因性疲憊症之臨床治療指引建議

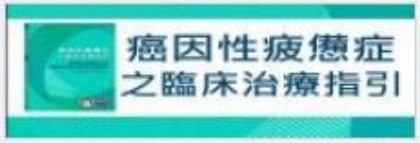
會員登入 MEMBER LOGIN

管理後台 | 會員專區 登出

管理員，歡迎登入本網站！

本月最新資訊

嚴重特殊傳染性肺炎相...



財團法人台灣癌症全人關懷基金會
TAIWAN TOTAL CANCER CARE FOUNDATION

…..touching cancer and aids patients through people caring

Cancer-related Fatigue Diagnosis & Management